Proposed Registration Decision PRD2017-13

Tolpyralate and Tolpyralate 400SC Herbicide

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Overview

Proposed Registration Decision for Tolpyralate

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of Technical Tolpyralate Herbicide and Tolpyralate 400SC Herbicide, containing the technical grade active ingredient tolpyralate, for post-emergent weed control in field corn (including corn grown for seed), sweet corn and popcorn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Technical Tolpyralate Herbicide and Tolpyralate 400SC Herbicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Canada.ca website at https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management.html.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on tolpyralate, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on tolpyralate, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Tolpyralate?

Tolpyralate is a new herbicidal active ingredient found in Tolpyralate 400SC Herbicide that has post-emergence activity on a variety of broadleaved and grassy weeds. While tolpyralate may be applied alone, it is recommended for use in tank mix with atrazine for post-emergent weed control in field corn (including corn grown for seed), sweet corn and popcorn.

Health Considerations

Can Approved Uses of Tolpyralate Affect Human Health?

Tolpyralate 400SC Herbicide, containing tolpyralate, is unlikely to affect your health when used according to label directions.

Potential exposure to tolpyralate may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient tolpyralate was of low acute toxicity by the oral, dermal and inhalation routes. Tolpyralate was non-irritating to the eyes and skin, and did not cause an allergic skin reaction.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.
[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*

The acute toxicity of the end-use product, Tolpyralate 400SC Herbicide, was low via the oral, dermal and inhalation routes of exposure. It was non-irritating to the eyes and skin and did not cause an allergic skin reaction.

Short- and long-term (lifetime) animal toxicity tests were assessed for the potential of tolpyralate to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment were effects on bodyweight and the liver, thyroid, pancreas, kidney, and nervous system. There was no indication that the young were more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate chronic (cancer and non-cancer) dietary intake estimates (food plus drinking water) revealed that the general population and all infants less than 1 year old, the subpopulation which would ingest the most tolpyralate relative to body weight, are expected to be exposed to less than 35% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from tolpyralate is not of health concern for all population subgroups.

Acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were equal to or less than 7.0% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was all infants (<1 year old).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using tolpyralate on field corn (including seed corn), sweet corn and popcorn are acceptable. Although an adjuvant was not included in the spray mixtures in the corn field trials, the overall residue chemistry data indicated that no increase in residues would be expected when tank mixed with methylated seed oil (MSO). Thus, it was concluded that the use of methylated seed oil as an adjuvant in tank mix with tolpyralate is acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

Occupational Risks From Handling Tolpyralate 400SC Herbicide

Occupational risks are not of concern when tolpyralate is used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Tolpyralate 400SC Herbicide, as well as field workers re-entering recently treated corn fields, can come in direct contact with tolpyralate

residues on the skin. Therefore, the label specifies that handlers mixing/loading and applying Tolpyralate 400SC Herbicide must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. The label also requires that workers do not enter treated corn fields for 12 hours after application except for seed corn, which requires workers to not enter treated corn fields for 2 days to perform detasseling.

Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the health risk to these individuals are not of concern.

Potential for bystander exposure is considered minimal and is expected to be significantly less than exposure estimated for workers. Based on the worker assessment, bystander exposure is not of concern.

Environmental Considerations

What Happens When Tolpyralate Is Introduced Into the Environment?

When used according to label directions, tolpyralate is not expected to pose an unacceptable risk to the environment.

Tolpyralate 400SC Herbicide, containing tolpyralate, can enter land and water habitats through spray drift and can enter water bodies through run-off when used as a foliar spray for weed control on sweet corn, field corn, and popcorn. In soil, tolpyralate degrades into breakdown products such as MT-2153 and is not expected to persist or accumulate over time. MT-2153 is more long lived and is expected to remain in the soil for a longer time than tolpyralate. Tolpyralate is soluble in water and can move through the soil, but is unlikely to reach ground water. MT-2153 may be able to reach ground water. Tolpyralate breaks down rapidly in water bodies. MT-2153 is long lived in water bodies where it may remain over time.

The vapour pressure and Henry's law constant of tolpyralate suggest that tolpyralate has low potential to volatilize from water and moist soil.

Tolpyralate is not expected to build up in plant and animal tissues.

Tolpyralate presents a negligible risk to most aquatic organisms (insects, fish and algae) and most terrestrial organisms including birds, mammals, earthworms, beneficial insects and honeybees. When tolpyralate is used at the labelled application rates, it could pose a risk to certain non-target aquatic and terrestrial plants if they are exposed to high enough concentrations. Therefore, mitigation measures, such as spray buffer zones (1-2 m size), are required to minimize potential exposure to non-target aquatic and terrestrial plants and, thereby, risk to the environment. When tolpyralate is used in accordance with the label and the required risk reduction measures are applied, the reduced environmental exposure is deemed adequate and risks are considered to be acceptable. Label statements informing users of the toxicity to non-target aquatic and terrestrial plants are required on product labels.

Value Considerations

What Is the Value of Tolpyralate 400SC Herbicide

Tolpyralate 400SC Herbicide is a new herbicidal end-use product that has post-emergence activity on a variety of economically important weeds that occur in field corn (including corn grown for seed), sweet corn and popcorn.

Tolpyralate 400SC Herbicide + methylated seed oil may be applied once or twice per year using ground application equipment. Tolpyralate 400SC Herbicide may be applied alone or in tank mix with atrazine for improved control of labelled weeds and broader spectrum weed control.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Tolpyralate 400SC Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with tolpyralate on the skin or through inhalation of spray mists, anyone mixing, loading and applying Tolpyralate 400SC Herbicide must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. The label also requires that workers do not enter treated corn fields for 12 hours after application except for seed corn, which requires workers to not enter treated corn fields for 2 days to perform detasseling. In addition, standard label statements to protect against drift during application were added to the label.

Environment

- Label statements informing users of the toxicity to non-target aquatic and terrestrial plants
- Standard statements to inform users of conditions that may favour run-off
- Precautionary label statements to inform users of the potential for leaching of the transformation product, MT-2153
- Spray buffer zones to protect habitats from drift

Next Steps

Before making a final registration decision on tolpyralate, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will

accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

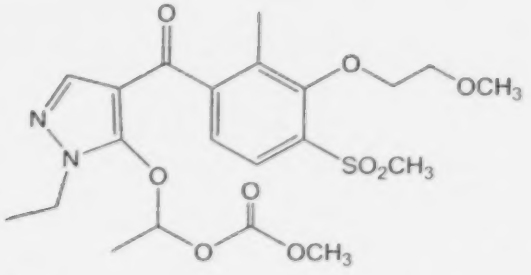
When the PMRA makes its registration decision, it will publish a Registration Decision on tolpyralate (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Tolpyralate

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Tolpyralate
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*RS*)-1-{1-ethyl-4-[4-mesyl-3-(2-methoxyethoxy)-*o*-toluoyl]pyrazol-5-yloxy}ethyl methyl carbonate
2. Chemical Abstracts Service (CAS)	1-[[1-ethyl-4-[3-(2-methoxyethoxy)-2-methyl-4-(methylsulfonyl)benzoyl]-1*H*-pyrazol-5-yl]oxy]ethyl methyl carbonate
CAS number	1101132-67-5
Molecular formula	$C_{21}H_{28}N_2O_9S$
Molecular weight	484.52
Structural formula	
Purity of the active ingredient	97.0%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Technical Tolpyralate Herbicide

Property	Result
Colour and physical state	Yellow solid
Odour	None
Melting range	127-129°C
Boiling point or range	N/A – decomposes after melting
Relative density	1.32
Vapour pressure at 25°C	5.9×10^{-4} Pa

Property	Result		
Henry's law constant at 20°C	9.6×10^{-3} Pa·m^3·mol^{-1}		
Ultraviolet (UV)-visible spectrum	conditions (pH)	λ_{max} (nm)	ε (L/mol.cm)
	0.1 M HCl (1.0)	259.6	14780
	purified water (6.1)	259.6	14980
	0.1 M NaOH (13.3)	253.0	11500
		285.4	7453
		310.2	8239
Solubility in water at 20°C	26.5 mg/L		
Solubility in organic solvents at 20°C	Solvent	Solubility (g/L)	
	n-heptane	0.03	
	xylene	18.3	
	1,2-dichloroethane	>250	
	acetone	148	
	methanol	11.6	
	n-octanol	0.6	
	ethyl acetate	92.3	
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 2.1		
Dissociation constant (pK_a)	No dissociation constant (pK_a) for the active ingredient was found in the pH range 1.1 – 13.2.		
Stability (temperature, metals)	The technical grade active ingredient is stable upon exposure to aluminum, aluminum acetate, iron, iron acetate, zinc and zinc acetate, and at elevated temperatures when stored at 54°C for 14 days.		

End-Use Product—Tolpyralate 400SC Herbicide

Property	Result
Colour	Off-white
Odour	Mild paint / acrylic
Physical state	Liquid
Formulation type	Suspension
Guarantee	400 g/L
Container material and description	500 mL to 200 L HDPE
Density	1.08 – 1.14 g/mL
pH of 1% dispersion in water	5.7 – 8.1
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Stable for 12 months in HDPE at 15-30°C
Corrosion characteristics	Not corrosive to its HDPE packaging
Explodability	Not explosive

1.3 Directions for Use

Tolpyralate 400SC Herbicide may be applied at 30-40 g a.i./ha +1% methylated seed oil (MSO) alone or in tank mix with a minimum of 0.56 kg a.i./ha atrazine for the control of labelled weeds in field corn, sweet corn, seed corn and popcorn. The inclusion of a high quality urea ammonium

nitrate (UAN) at 12.5-25 L/1000 L or a spray grade ammonium sulfate (AMS) at 8.4-20.4 kg/1000 L may improve overall weed control. Application may be made by ground boom in 140-170 L/ha water post-emergence to the crop and weeds, up to the six leaf stage of corn. Tolpyralate 400SC Herbicide is rainfast within one hour of application.

1.4 Mode of Action

Tolpyralate 400SC Herbicide contains 400 g/L of Tolpyralate which is a 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor. This mode of action belongs to the Weed Science Society of America (WSSA)/Herbicide Resistance Action Committee (HRAC) mode of action Groups 27 and F2, respectively. The application of this herbicide type results in bleaching of plant tissues as the synthesis of pigments is interrupted in susceptible plants.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method JSM0433 in plant matrices and Method D96518 in animal matrices) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1. In addition, acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled crop samples analyzed with the plant enforcement method. For the livestock enforcement method, extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled livestock matrices was not required for the enforcement method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Tolpyralate is a member of the benzoylpyrazole, diketone family of herbicides. A detailed review of the toxicological database for tolpyralate was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to tolpyralate.

Toxicokinetic data consisted of studies in which rats received phenyl- or pyrazole-labelled tolpyralate in a single oral low and high dose or as a single low dose following 14 days of receiving a low dose of unlabelled tolpyralate. Tolpyralate was quickly and extensively absorbed and rapidly excreted. There was no evidence of saturation of the metabolic pathways. Tissue concentrations 96 hours after dosing were less than 5% of the administered dose. The highest concentrations were in the gastrointestinal (G.I.) tract, liver, kidney and carcass, although measurable amounts were found in the muscle. Excretion occurred primarily via the urine, with faecal excretion divided evenly between absorbed and unabsorbed compound as indicated in the biliary excretion study. Elimination was essentially complete by 96 hours post-dosing. The position of the radiolabel did not have significant impact on the toxicokinetic profile. There were few differences between sexes or doses.

The proposed metabolic pathway involved dealkylation and subsequent conjugation with glucuronic acid. Absorbed tolpyralate was completely metabolised and the major metabolites were TAT-834 and MT-2153 with MMTA present in the urine before being quickly broken down (Appendix I, Table 2). Metabolism in the liver is similar in mouse, rat and human microsomes.

In acute toxicity testing in rats, tolpyralate and Tolpyralate 400SC Herbicide were of low toxicity via the oral, dermal and inhalation routes. Tolpyralate and Tolpyralate 400SC Herbicide were non-irritating to the eyes and skin of rabbits. They were not dermal sensitizers in guinea pigs according to the Maximization Method or in mice according to the Localized Lymph Node Assay.

The main target in laboratory animals is the eye. In rats, crystals accumulate in the eye leading to corneal opacity and keratitis at the lowest dose tested following as little as 28 days of dosing and thereafter to squamous cell eye tumours in males at the LOAEL following two years of dosing. In dogs, opacity and keratitis of the eyes were seen in females at the highest dose tested. No effects in the eyes were observed in the mouse. Tolpyralate is an inhibitor of the enzyme 4-hydroxy-phenylpyruvate dioxygenase (HPPD); this enzyme is important in the metabolism of the amino acid, tyrosine. Prolonged inhibition of this enzyme results in an increase in plasma tyrosine levels (tyrosinemia). Excess tyrosine in the blood is metabolized to phenolic acids and excreted in the urine. Following inhibition of HPPD, the extent of the tyrosinemia is controlled by another catabolic enzyme, tyrosine aminotransferase (TAT). There is a direct correlation

between tyrosinemia and ocular toxicity. Published literature indicates that tyrosine accumulates in the anterior aqueous humor and, in excess, forms crystals which are then deposited in the cornea. The threshold plasma tyrosine concentration for ocular effects in all species is ~1000 nmol/mL, which must be exceeded for a prolonged period of time before ocular lesions develop. Mode of action studies confirmed that single exposure to a high-dose of tolpyralate elevated plasma tyrosine levels in female rats by 26-fold with a peak at 24 hours, in female rabbits by 20-fold with a peak at 24 hours and in female mice by 13-fold with a peak at 8 hours. Thus, with respect to human relevance, the mouse is a better quantitative model than the rat or dog for tyrosine-induced eye lesions, since TAT and the resulting plasma tyrosine concentrations are similar between mice and humans. As a result, effects observed on eyes in the rat and dog studies are qualitatively, but not quantitatively relevant to humans.

Following short- and long-term dietary exposure, the target organs were the liver and kidneys in mice, rats and dogs, the neural tissue in mice and rats and the thyroid and pancreas in rats only. Body weights were decreased in male mice and dogs and in male and female rats compared to control animals at the highest dose tested or at the mid-high dose in male rats in long-term studies. An increase in mortality was noted in male mice in the chronic toxicity study at the highest dose tested. In both mice and rats, loss of tactile hair was noted in the long-term dietary studies. Soiled and wetted fur and callouses were also noted in rats in the long-term studies.

There was evidence of increased toxicity with increased duration of dosing in the database. Clinical chemistry changes and liver hypertrophy and necrosis were observed at lower doses in longer-term studies than the short-term studies. In dogs, liver changes were noted only in the 1-year study and at the high dose. Effects in the kidney were more profound in male rats than females and following longer-term dosing than short-term dosing. Following short-term dietary exposure, effects included increased urinary ketones and kidney weight, while longer-term dosing resulted in tubular basophilic change and urinary crystal formation. Hyaline droplet formation, occurring at the limit dose in the 90-day rat study was considered relevant to the human health hazard assessment in the absence of staining to confirm a species-specific mode of action.

Degeneration of the sciatic nerve was noted in the female mouse and both sexes of rat in the long-term dietary studies. In the mouse, the effect was observed only at the highest dose tested. In rats, it occurred in males at the LOAEL following one year of treatment and in both sexes at the LOAEL following two years of treatment. Brain weights were decreased in male rats in the carcinogenicity study at the LOAEL as well. At the high dose in the rat carcinogenicity study, there was an increase in atrophy of striated muscle fibre in males and a decrease in spontaneous activity in females. In the long-term studies, vacuolation of the cerebellum was noted in males at the LOAEL following one year of dosing and in females following two years of dosing in the carcinogenicity study. Females in the chronic toxicity study exhibited vacuolation of the cerebellum at the highest dose tested following one year of dosing. However, there was no evidence of neurotoxicity in either the acute or the subchronic neurotoxicity study, indicating that the effects on neurological tissue only occurred following extended high-dose exposure.

Other noteworthy findings were observed in the rat, mouse and dog. Follicular cell hypertrophy of the thyroid was noted in the 28-day, 90-day and 1-year rat toxicity studies, with colloid degeneration of the thyroid noted in both sexes at the LOAEL in the carcinogenicity study. Male rats were more sensitive to treatment-related effects on the pancreas than females, with similar effects seen at lower doses in males in the 28-day, 90-day and 1-year oral rat toxicity studies. Acinar single cell necrosis was noted in the short-term dietary studies and acinar cell atrophy/fibrosis and fat infiltration of the pancreas was observed in the long-term dietary studies. Treatment-related changes specific to the mouse consisted of an increase in calculi of the gallbladder in the long-term dietary study in all tolpyralate-treated groups. In the 1-year dog study, there was an increase in conjunctival edema and congestion, abnormal stool, increased fibrinogens, decreased mean corpuscular haemoglobin (MCH), granulopoeisis of bone marrow with increased neutrophils, and an increase in mild hyperplasia of the interior iliac lymph nodes in males at the high dose.

Results of a standard genotoxicity battery, consisting of bacterial gene mutation, chromosome aberration, mammalian gene mutation, and unscheduled DNA synthesis assays, indicated that tolpyralate was not genotoxic. There was a treatment-related increase in eye tumours in males noted in the two-year rat dietary toxicity study; however, this was not considered relevant to the human health hazard assessment, as the mouse was considered a more relevant model for potential human tolpyralate toxicity. There was no other evidence of carcinogenicity in the rat studies and no evidence of carcinogenicity in the mouse study.

Signs of dermal irritation were noted in the 28-day repeat-dose dermal toxicity study; however, no signs of systemic toxicity were noted up to the limit dose of testing.

In the dietary reproductive toxicity study in rats, F1 parental males exhibited an increase in kidney nephropathy at the mid-dose, and increases in mortality and changes to body weights, kidneys, and liver occurred in males and females at the highest dose tested. Reproductive toxicity occurred only at the highest dose tested and consisted of an increased number of days until mating and decreased pup viability on Day 0 in both the P and F1 generations, and decreased gestational index in F1. Effects on the offspring occurred only in the presence of parental toxicity and consisted of an increased number of pups lost or killed in extremis in the F1 and F2 generations, an increased incidence of pale kidneys, renal pelvic dilatation, renal cysts and small kidneys in the F1 and F2 generations, and an increased age of sexual maturation in both males and females. A developmental gavage study was performed in rats to investigate whether the kidney effects in the offspring could be attributed to the elevated tyrosine levels. It was determined that this study was not conducted in a manner that would rule out relevancy of this effect to the human health hazard assessment.

In the rat developmental gavage toxicity study, maternal toxicity consisted of increased red sebum and body weight loss in the first three days of treatment and decreased food consumption over the first 6 days of treatment. At these maternally toxic doses, fetal effects consisted of decreased weights and increased fetuses with variations, such as branched rib cartilage and 27 presacral vertebrae. In the rabbit developmental gavage toxicity study, a slight increase in the number of litters with total resorptions occurred at the highest dose tested. At the same dose, an increased incidence of skeletal variations consisting of supernumerary ribs and 27 presacral vertebrae, and a decrease in male fetal body weights also occurred.

There was no evidence of immunotoxicity in a PFC assay in female mice following dietary dosing for 28 days up to the limit dose.

There was decreased rearing and activity in male rats during Day 1 of the acute gavage neurotoxicity study, as well as a decrease in body weight gain from Days 1 – 8 at the highest dose tested; however, this change was attributed to systemic toxicity as opposed to neurotoxicity. There were no signs of direct neurotoxicity in the subchronic dietary neurotoxicity study.

Studies on the metabolites indicated that MT-2153 and MMTA were of low acute oral toxicity in rats and non-genotoxic in the Ames, in vitro mammalian cell and chromosome aberration assays for MMTA and Ames test for MT-2153.

The identities of the studied metabolites are summarized in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with tolpyralate and its associated end-use products and metabolites, are summarized in Appendix I, Tables 3, 4 and 5. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 6.

Incident Reports

Tolpyralate is a new active ingredient pending registration for use in Canada and the United States; as such, there are no incident reports in the PMRA or American databases. Once products containing tolpyralate are registered, the PMRA will monitor for incident reports.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of studies, including developmental toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats, was available for tolpyralate.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. There was a slight increase in the number of litters with total resorptions in the rabbit developmental toxicity study. While resorptions are considered a serious effect, concern for this finding was tempered by the small increase in incidence and the large (100-fold) difference between the LOAEL and the NOAEL for this effect. Other changes consisted of minor developmental effects (increased incidence of skeletal variations) in the rat and rabbit developmental toxicity studies; however, these effects occurred in the presence of maternal toxicity. In the two-generation rat reproductive toxicity study, effects on the young included decreases in survival (a serious effect), as well as effects on the kidney and delayed sexual maturation in both sexes at the highest dose tested, however; these effects occurred in the presence of maternal toxicity (kidney, bodyweight and eye effects and increased mortality). Overall, endpoints in the young were well-characterized and the endpoints selected for risk assessment provided adequate margins to the effects noted above. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose (ARfD)

General Population

To estimate acute dietary risk (1 day), the rat developmental toxicity study with a NOAEL of 10 mg/kg bw/day was selected for risk assessment. At the LOAEL of 500 mg/kg bw/day, body weight loss was observed following the first 3 days of dosing and was therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw}}{100} = 0.1 \text{ mg/kg bw of tolpyralate}$$

3.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the long-term rat study with a NOAEL of 0.9 mg/kg bw/day was selected for risk assessment. At the LOAEL of 97 mg/kg bw/day, loss of fur and clinical signs of toxicity, as well as liver, thyroid, pancreatic, kidney and neuropathological effects were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.9 \text{ mg/kg bw/day}}{100} = 0.009 \text{ mg/kg bw/day of tolpyralate}$$

The ADI results in a margin of 555 to the NOAEL of 5 mg/kg bw/d for the slight increase in total resorptions in the rabbit developmental toxicity study and a margin of 390 to the NOAEL of 3.5 mg/kg bw/day for offspring effects in the rat reproductive toxicity study.

Cancer Assessment

There was a treatment-related increase in squamous cell carcinomas of the eye in male rats in the 2-year carcinogenicity study. However, it was determined that the tumours in the rat study were qualitatively but not quantitatively relevant to humans, based on the mode of action for HPPD inhibitors. A threshold approach was considered appropriate for these tumours, with a margin of 9333 between the dose at which tumours were observed and the ADI.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Exposure to tolpyralate is expected to be mainly via the dermal and inhalation routes for chemical handlers and through the dermal route for postapplication re-entry workers. Exposure is expected to be short- to intermediate-term in duration since the product can be applied twice during the growing season by farmers and over 30 days per season by custom applicators.

Short- and Intermediate-term Dermal and Inhalation

For short- and intermediate-term exposures via the dermal and inhalation routes, the NOAEL of 1.34 mg/kg bw/day from the 90-day oral rat toxicity study was selected for risk assessment. At 113 mg/kg bw/day, there were effects on urinalysis and clinical chemistry parameters, increased liver and kidney weights and increased incidences of thyroid follicular cell hypertrophy and single cell necrosis in the pancreas. The use of the 90-day NOAEL provides an adequate margin to the LOAEL of 3.1 mg/kg bw/day for kidney nephropathy observed in F1 males in the reproductive toxicity study, which may be due to in utero exposure. The 28-day dermal toxicity study did not address this endpoint of concern (namely, in utero exposure), therefore this study was not selected for the dermal risk assessment, and a short-term inhalation study was also not available for a route-specific risk assessment.

The target Margin of Exposure (MOE) for these occupational scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

An in vitro dermal absorption study using human skin was reviewed and considered to be acceptable but could not be used on its own for estimating occupational exposure.

The extent of absorption of radioactivity following dermal application of [^{14}C]-tolpyralate in a soluble concentrate (SC) formulation were investigated in an in vitro absorption study on human skin. [^{14}C]-tolpyralate (99.1% radiochemical purity) was applied at two doses topically to human skin excised from seven male and female donor cadavers. The high dose was equivalent to the Tolpyralate 400SC Herbicide formulation (nominally 400 g a.i./L) and the lower dose was equivalent to the in use application rate of the product (nominally 0.25 g a.i./L). Twelve flow-through diffusion cells were prepared at each dose level using 2-3 skin sample replicates per donor. The skin samples were exposed to the test material for six hours, after which time the remaining dose was washed off the skin. Receptor fluid samples were collected hourly for the duration of the experiment (24 hours). At the end of the experiment, the skin samples were tape stripped to remove the residual surface dose and the stratum corneum.

The total amounts of radioactivity in the receptor fluid after 24 hours were 0.1% and 0.3% at the high and low dose levels, respectively. For the high dose, the skin swabs taken at six hours contained most of the applied dose (89.7%), with 0.3% removed in the surface tape strips (strips 1-2) taken after 24 hours. Tape strips taken to remove the stratum corneum (strips 3-14) contained 0.1% of the dose. The dose remaining on the skin was below the limit of quantification (LOQ). For the low dose, the skin swabs taken at 6 hours contained 98.3% of the dose, with a further 0.9% of the dose removed in the surface tape strips taken at 24 hours. Tape strips taken to remove the stratum corneum contained 0.5% of the dose. The dose remaining on the skin was below the LOQ. The material recovered in the surface strips and stratum corneum after 24 hours was considered available for absorption. Therefore the total amounts of radioactivity potentially absorbable by 24 hours were 0.5% and 1.7% at the high and low dose levels, respectively. No corrections were made for recovery as all recoveries were above 90% and found to be acceptable.

The dermal absorption values derived solely from the in vitro dermal absorption data from human skin cannot be used for human health risk assessment. However, the human in vitro data were used in a weight-of-evidence approach to refine the dermal absorption value. Criteria investigated included an examination of the physical/chemical (phys-chem) properties of tolpyralate, a comparison of dermal and oral acute toxicology studies and a review of other 4-hydroxyphenylpyruvate dioxygenase (HPPD) class chemicals.

On their own the phys-chem properties are insufficient to justify the reduction of the dermal absorption factor because of the n-octanol-water partition coefficient indicating potential high absorption. A comparison of the dermal and oral rat toxicity studies showed no signs of ocular opacity/keratitis effects in the dermal studies, which are the most sensitive systemic toxicity endpoint in rats, thus indicating low dermal absorption. A comparison to chemicals in the same class (HPPD inhibitors) found dermal absorption values from in vivo rat studies of less than 10%. Therefore, based on the low dermal absorption values of human skin in vitro, the likelihood of lower dermal absorption based on the lack of ocular effects via the dermal route in rats in vivo

and the fact that other HPPD inhibitors all have dermal absorption values of less than 10%, the default dermal absorption factor of 100% can be reduced to 50% for tolpyralate.

3.4.1.2 Dislodgeable Foliar Residue

A chemical-specific dislodgeable foliar residue (DFR) study in corn was conducted at three sites within representative corn growing regions, in North Carolina (NC), North Dakota (ND) and Missouri (MO), on corn leaves following treatment of the growing crop with Tolpyralate 400SC Herbicide. One application was made to corn at a target application rate of 100 g a.i./ha. Leaf punch samples (5 cm^2 each side, 40 per sample) were taken prior to the application and at one and eight hours, and 1, 2, 3 - 4, 5, 9 - 10, 13 - 14, 21, 27 - 28 and 35 days after application.

At the NC site, the corrected mean dislodgeable residue was 0.121 $\mu g/cm^2$ at one hour after application and reached a maximum of 0.126 $\mu g/cm^2$ at eight hours after application. The residue was below the limit of quantification (LOQ) by Day 4. At the ND site, the highest mean dislodgeable residue was 0.211 $\mu g/cm^2$ at one hour after application. The residue decreased to 0.072 $\mu g/cm^2$ by Day 3 and was below the LOQ by Day 5. At the MO site, the mean dislodgeable residue was 0.119 $\mu g/cm^2$ at one hour after application and reached a maximum of 0.128 $\mu g/cm^2$ at eight hours after application. The residue decreased to a mean of 0.0036 $\mu g/cm^2$ by Day 10 and was less than the LOQ by Day 14.

The half-life ($t_{1/2}$) for dislodgeable residues of tolpyralate from corn leaves was estimated to be approximately 1 to 2 days at all three sites.

For the postapplication exposure assessment on corn, the data from the Missouri location was used, with a predicted peak residue value of 13% and a daily dissipation rate of 28%, resulting from the calculated dissipation equation ($r^2 = 0.98$). This site was chosen over the North Dakota site because of there being no significant difference in the weather between the two sites and the better r^2 value for Missouri (0.98 vs 0.81 for ND).

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Tolpyralate 400SC Herbicide during mixing, loading and application. Exposure to workers mixing, loading and applying Tolpyralate 400SC Herbicide is expected to be intermediate in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders and applicators applying Tolpyralate 400SC Herbicide to corn fields using groundboom application equipment.

The exposure estimates are based on mixers/loaders/applicators wearing a single layer and chemical-resistant gloves.

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers were estimated using the Agricultural Handlers Exposure Task Force (AHETF). AHETF are compilations of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 50% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Dermal and inhalation exposure estimates were compared to the relevant tolpyralate toxicological endpoint (no observable adverse effect level [NOAEL] = 1.34 mg/kg bw/day) to obtain the combined margins of exposure (MOEs); the target MOE is 100. Tables 3.4.2.1-1 & 3.4.2.1-2 present the AHETF unit exposure values and estimates of exposure and risk, respectively. Acceptable MOEs were calculated for workers who wear the proposed personal protective equipment (PPE), use the engineering controls, and follow the restrictions on the product label.

Table 3.4.2.1-1 AHETF unit exposure estimates for mixer/loaders and applicators handling Tolpyralate 400SC Herbicide (µg/kg a.i. handled)

Scenario		Dermal	Dermal absorbed*	Inhalation†	Total unit exposure¶
Mixer/loader AHETF estimates					
A	Open Mix/Load Liquids (Single layer, CR gloves)	58.50	29.25	0.63	29.88
Applicator AHETF estimates					
B	Open Cab Groundboom Liquid Application (Single layer, CR gloves)	25.40	12.7	1.68	14.38
Mixer/loader + applicator AHETF estimates					
A+B	Open Mix/Load Liquids & Open Cab Groundboom Liquid Application (Single layer, CR gloves)	83.90	41.95	2.31	44.26

* Adjusted with dermal absorption factor 50%

† Light inhalation rate

¶ Total unit exposure: Dermal exposure + inhalation exposure

Table 3.4.2.1-2 Mixer/loader/applicator risk assessment for chemical handlers

Exposure scenario	Unit exposure (µg/kg a.i. handled)*	ATPD (ha/day)†	Rate (kg a.i./ha)	Daily exposure (mg/kg bw/day)‡	MOE (target 100) ¶
PPE: (Single layer, CR gloves)					
Farmer (M/L/A)	44.26	107	0.04	2.37	566
Custom (M/L)	29.88	360		5.38	249
Custom (A)	14.38	360		2.59	518
Custom (M/L/A)	44.26	360		7.97	168

* Unit exposure based on AHETF from Table 3.4.2.1-1
† Default Area Treated Per Day Tables (2015)
‡ Daily exposure = (Unit exposure [µg/kg a.i.] × ATPD [ha] × Rate [kg/ha]) / (80 kg bw × 1000 µg/mg)
¶ Based on NOAEL = 1.34 mg/kg bw/day, target MOE = 100

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Postapplication dermal exposure may occur when workers enter treated corn fields to perform various activities. The duration of exposure is considered to be short- to intermediate-term as these activities may occur throughout the growing season.

Dermal exposure to workers entering treated areas is estimated by coupling chemical-specific dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients.

The exposure estimates were compared to the tolpyralate toxicological endpoint (NOAEL = 1.34 mg/kg bw/day) to obtain the MOE; the target MOE is 100. Since these values exceed the target MOE of 100 (Table 3.4.2.2-1) for corn (with the exception of detasseling and hand harvesting), the level of postapplication exposure is not of health concern. A 2-day restricted entry interval (REI) is required to protect re-entry workers for corn detasseling only since hand harvesting cannot occur for 35 days after application (PHI = 35 days).

Table 3.4.2.2-1 Postapplication exposure and risk estimate for tolpyralate on day 0 after the last application

Re-entry activity	Peak DFR (µg/cm^2)*	Transfer coefficient (cm^2/hr)†	Dermal exposure (mg/kg bw/day)‡	MOE (target 100)¶	REI◊
Hand weeding	0.052	70	0.000	7306	12 hours
Scouting	0.052	1100	0.003	465	12 hours
Hand set irrigation	0.052	1750	0.005	292	12 hours
Hand harvesting/detasseling	0.052	8800	0.023	58	N/A
	0.027		0.012	111	2 days

* Calculated using the predicted peak residue value of 13% and a daily dissipation rate of 28%
† Transfer coefficients obtained from PMRA Agricultural TCs Table (12.22.2016)
‡ Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours × 50% dermal absorption) / (80 kg bw × 1000 µg/mg)
¶ Based on a NOAEL of 1.34 mg/kg bw/day, target MOE = 100
◊ Minimum REI is 12 hours to allow residues to dry

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

Tolpyralate 400SC Herbicide is not a domestic class product; therefore, a residential handler assessment was not required.

3.4.3.2 Postapplication Exposure and Risk

Tolpyralate 400SC Herbicide is not a domestic class product; therefore, a residential handler assessment was not required.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application to agricultural crops is permitted only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in corn is tolpyralate and in animal commodities is tolpyralate including the metabolite MT-2153 (1-ethyl-5-hydroxy-1*H*-pyrazol-4-yl-3-(2-methoxyethoxy)-4-mesyl-2-methylphenyl ketone). The data gathering/enforcement analytical method is valid for the quantitation of tolpyralate and MT-2153 residues in plant and livestock matrices. The residues of tolpyralate and MT-2153 are stable in corn forage and grain for up to 12 months when stored frozen at -15°C. The raw agricultural commodity, field corn grain, was processed and residues did not concentrate in any fractions (dust, starch, oil, grits, meal and flour). Quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Crop field trials conducted throughout Canada and the United States using end-use products containing tolpyralate at approved rates in or on field corn (including seed corn), sweet corn and popcorn are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis for tolpyralate: 100% crop treated, default processing factors (where available), and the recommended MRLs for field corn, sweet corn, popcorn and all animal commodities. The basic chronic dietary exposure from all

supported tolpyralate food uses (alone) for the total population, including infants and children, and all representative population subgroups is equal to or less than 11.0% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to tolpyralate from food and drinking water is 10.4% (0.000938 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants at 34.4% (0.003092 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for tolpyralate: 100% crop treated, default processing factors (where available), and residues in/on field corn, sweet corn, popcorn and animal commodities at MRL levels. The basic acute dietary exposure (food alone) for all supported tolpyralate commodities is estimated to be 0.61% (0.000613 mg/kg bw) of the acute reference dose (ARfD) for the total population (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: ≤7.0% of the ARfD for the total population and all representative population subgroups. The highest exposure and risk estimate is for all infants at 7.0% (0.006996 mg/kg bw) of the ARfD.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for tolpyralate consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.4-1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Field corn, popcorn grain, sweet corn kernels plus cob with husks removed	0.01
Eggs; fat, meat and meat byproducts of cattle, goat, hog, horse, poultry and sheep; milk	0.02

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 7 and 8.

3.6 Exposure From Drinking Water

3.6.1 Concentrations in Drinking Water

Tolpyralate and MT-2153 were modelled considering their transformation relationship in soil and water. Their drinking water estimated environmental concentrates (EEC) were then added up to calculate the combined residue EECs.

3.6.2 Modelling Estimates - Application Information and Model Inputs

Tolpyralate, also known as SL-573, is a new herbicide proposed for use on corn. The maximum proposed yearly application rate is two applications of 40 g a.i./ha with an interval of 14 days between applications. Application information and the main environmental fate characteristics used in the model are summarized in Table 3.6.2-1.

Table 3.6.2-1 Major groundwater and surface water model inputs for Level 1 assessment of tolpyralate

Type of Input	Parameter	Value	
Application Information	Crop(s) to be treated	Corn	
	Maximum allowable application rate per year (g a.i./ha)	80	
	Maximum rate each application (g a.i./ha)	40	
	Maximum number of applications per year	2	
	Minimum interval between applications (days)	14	
	Method of application	CAM 2 (ground foliar)	
Environmental Fate Characteristics	**Compound**	**Tolpyralate**	**MT-2153**
	Hydrolysis half-life at pH 7 (days)	31.45	Stable
	Photolysis half-life in water at 40°N latitude (days)	7.5	724.63
	Adsorption K_{oc} (mL/g)	27.53 (20^{th} percentile of 5 K_{oc} values)	55.44 (20^{th} percentile of 5 K_{oc} values)
	Aerobic soil biotransformation half-life at 20°C(days)	0.92 (90^{th} percentile confidence on the mean of 4 half-lives)	207.3 (90^{th} percentile confidence on the mean of 4 half-lives)
	Aerobic aquatic biotransformation half-life at 20°C (days)	1.77 (longer of 2 half-lives in entire system)	206.14 (longer of 2 half-lives in entire system)
	Anaerobic aquatic biotransformation half-life at 20°C (days)	2.61 (longer of 2 half-lives in entire system)	430.38 (longer of 2 half-lives in entire system)

3.7 Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

Estimated environmental concentrations (EECs) of the combined residue (tolpyralate and its major transformation product MT-2153) in potential drinking water sources (groundwater and surface water) were estimated using the PWC model to simulate both leaching through a layered

soil profile over a 50-year period, where concentrations were calculated from the average concentrations in the top 1m of the water table or pesticide runoff from a treated field into an adjacent water where EECs are the average concentration in the water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application timing, and geographic scenario. These EEC estimates may allow for future use expansion into other crops at this application rate. Table 3.6.2-1 lists the application information and main environmental fate characteristics used in the simulations. Six initial application dates between May and July were modelled. The models were run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 3.7-1 below.

Table 3.7-1 Level 1 estimated environmental concentrations of the combined residue of tolpyralate and its major transformation product MT-2153 in potential drinking water

Use pattern	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
2 × 40 g a.i./ha	37	37	2.7	0.43

Notes:
1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of daily peak concentrations
4 90th percentile of yearly average concentrations

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Tolpyralate is soluble in water. Based on its low vapour pressure and Henry's law constant, volatilization of tolpyralate from moist soil or water surfaces is unlikely to be a significant route of dissipation in the environment.

In the terrestrial environment, photolysis is not a major route of transformation of tolpyralate in soil (DT_{50} = 40.8 days with continuous irradiation); tolpyralate transformed more rapidly in the dark than when under irradiation. MT-2153 and CO_2 (CO_2 was only produced in irradiated soil) were the only major photolytic transformation products. Two minor products, identified as Component 2 and Component 3, were also produced in soil photolysis. At environmentally relevant pH levels, hydrolysis is not a major route of transformation for tolpyralate; MT-2153 was the only (major) hydrolytic transformation product. Biotransformation is a major route of dissipation of tolpyralate in aerobic soil; tolpyralate undergoes rapid transformation (half-lives ranging from 0.2 to 1.2 days) under aerobic conditions to form several major transformation products, namely, MT-2153, MMTA, Ph-A and CO_2. MT-2153 is more persistent than

tolpyralate (half-lives ranging from 70 to 225 days) while the half-life of MMTA was similar to that of tolpyralate. Minor soil biotransformation products observed were identified as Ph-B, Py-A, Py-B, Py-C, Met-A and Met-B. A high amount of unextracted residues are also observed in the photolysis and biotransformation of tolpyralate in soil but available data suggests that these residues are products of microbial degradation rather than the parent tolpyralate. Transformation of tolpyralate in anaerobic soil is expected to be similar to aerobic soil; however, this could not be definitively confirmed as anaerobic conditions were not maintained in the anaerobic soil study. The transformation product, MT-2153, was shown to be stable to hydrolysis and was more persistent than tolpyralate (half-lives ranging from 70 to 225 days) in aerobic soil. MMTA was shown to be rapidly transformed in soil, with a half-life of 1.1 days. Under field conditions, tolpyralate was not persistent, with field half-lives of 1.5 to 2.8 days in two North American sites conducted in a Canadian relevant ecoregion (North Dakota and New York). MT-2153 was the major transformation product observed under field conditions. MT-2153 was also not persistent in the field, with half-lives of 3.6 and 17.8 days. Two other North American field sites (Illinois and North Carolina) show similar field profiles for tolpyralate and MT-2153.

Mobility studies show that tolpyralate is very highly mobile, with K_{oc} values between 15 and 90. Mobility studies also show that MT-2153 is very highly mobile (K_{oc} values between 40 and 140). In the field, both tolpyralate and MT-2153 residues were not detected below the plough layer (a depth of 15 cm) of the soil. The criteria of Cohen et al. and the groundwater ubiquity score (GUS) are indicative that tolpyralate is unlikely to leach into ground water. Although MT-2153 was not detected below the plough layer in field studies, all other criteria suggest that MT-2153 may have the potential to leach into ground water. The terrestrial environmental fate data for tolpyralate are summarized in Appendix I, Table 9.

Hydrolysis and photolysis at environmentally relevant pHs in the aquatic environment are not major routes of transformation for tolpyralate (DT_{50} values = 31.5 and 7.5 days, respectively). However, hydrolysis of tolpyralate results in the formation of one major transformation product, MT-2153, while aquatic photolysis results in the formation of MT-2153 and twenty unidentified transformation products, of which four were major transformation products. These unidentified major transformation products were designated as EVC-005 (present as two isomeric forms) and EVC-006 (present as two isomeric forms). Aquatic biotransformation is a major route of dissipation of tolpyralate with half-lives in the water/sediment system ranging between 1.4 to1.8 days. MT-2153 was the only major aquatic biotransformation product detected in water/sediment systems. Met A, Met B and an unknown polar compound were observed in minor quantities. Similar to the terrestrial environment, high amounts of unextractable residues are observed in water/soil systems. Unlike tolpyralate, MT-2153 is persistent in aerobic aquatic environments with half-lives ranging between 190 to 225 days. Transformation of tolpyralate in the anaerobic aquatic environment is expected to be similar to aerobic soil; however, this could not be definitively confirmed as anaerobic conditions were not maintained in the anaerobic aquatic study. The aquatic environmental fate data for tolpyralate is summarized in Appendix I, Table 10.

Tolpyralate has a low potential to bioaccumulate in biota as the log Kow value was reported to be 1.9. Modelling estimates indicate that MT-2153 (log K_{ow} 1.7) shows a low potential to bioaccumulate.

An atmospheric model predicted an atmospheric half-life of less than one day. However, there is high amount of uncertainty around this estimate as a high fraction of tolpyralate is expected to sorb to airborne particles which will decrease the availability of tolpyralate to be degraded by atmospheric oxidation.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1 for most species, 0.4 (acute) and 1 (chronic) for pollinators, and 2 for beneficial arthropods (predatory mite and parasitoid wasp). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk (see Appendix III). A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment of tolpyralate was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of ½ and 1/10 the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for terrestrial invertebrates, birds and mammals when calculating RQs. No uncertainty factors are applied to chronic NOEC endpoints.

Species sensitivity distribution (SSD) analysis was conducted when sufficient acute toxicity data are available to determine hazardous concentration to five percent of species (HC_5) using the software program ETX 2.1. The HC_5 is the concentration which is theoretically protective for 95% of species. At the HC_5 exposure level, five percent of all species may be exposed to a concentration which exceeds the toxicity value. The variability around the fraction of species affected (FA value) is indicated by the lower and upper confidence limits (90% CI), which indicates the minimum and maximum percent of species that may be affected at the HC_5 value.

A summary of the toxicity data of tolpyralate to non-target organisms is presented in Appendix I, Tables 12 and 13 while the screening level risk assessment of tolpyralate and MT-2153 to non-target organisms except for birds and small wild mammals is presented in Appendix I, Tables 14 and 15, respectively.

Earthworms and collembola: Tolpyralate and its major transformation product, MT-2153, and an end-use formulation of tolpyralate, SL-573 400SC, were not acutely or chronically toxic to earthworms up to the highest concentration tested. MT-2153 was not chronically toxic to collembola. The screening level risk assessment was determined by comparing this value to the EECs for the highest use rate scenario of tolpyralate on corn (40 g a.i./ha × 2 applications). The LOC was not exceeded for earthworms and collembola.

Bees (pollinators): The effect of tolpyralate and an end-use formulation of tolpyralate, SL-573 400SC, were observed on honey bees on an acute oral, acute contact and on a chronic basis. The effect of tolpyralate was also observed on honey bee larvae on an acute and chronic basis. Acute oral exposure of tolpyralate to honey bees resulted in treatment related mortality of 2% in the highest test concentration. No other treatment related effects were observed. No treatment related effects were observed in the acute contact or chronic honey bee studies. Acute and chronic exposure of tolpyralate to honey bee larvae resulted in treatment related reduction in larval survival and adult emergence (92 and 89%, respectively) at the highest test concentration. The LOC (acute and chronic exposure) was not exceeded for both adult and larval honey bees.

Beneficial arthropods: Acute exposure of the tolpyralate formulated product, SL-573 100OD, when applied on glass plates, affected the survival but not the fecundity of the parasitic wasp, *Aphidius rhopalosiphi*, and the predatory mite, *Typhlodromus pyri*. MT-2153 did not affect the survival of adult predatory mites (*Hypoaspis aculeifer*) but reproduction was affected at the highest concentration tested. The LOC for tolpyralate was not exceeded for both the parasitic wasp and the predatory mite while the LOC for MT-2153 was not exceeded for the predatory mite.

Non-target plants: The effect of tolpyralate to non-target plants was determined through the exposure of the formulated end-use product, SL-573 400SC, with a seedling emergence and vegetative vigour assay using standard crop species. Tolpyralate had similar toxicity to the 12 crop plants which were tested based on seedling emergence and vegetative vigour, the latter being somewhat more sensitive. Tolpyralate was observed to reduce the dry weight of several species in both seedling emergence (cabbage, carrot, cucumber, lettuce, onion, sugarbeet and tomato) and vegetative vigour (lettuce, soybean and sugarbeet) studies. Using the HR_5 value for the formulated end-use product from the SSD of ER_{50} values for seedling emergence (RQ =

26.70) and vegetative vigour (RQ = 55.16), the calculated RQs exceeded the LOC at the screening level.

The risk to terrestrial non-target plants was further characterized by examining off-field exposure from drift. Based on the RQs calculated using the off-field EECs from drift, the LOC for non-target terrestrial plants was still exceeded for both seedling emergence (RQ = 1.60) and vegetative vigour (RQ = 3.31). Spray buffer zones will be required on product labels to protect terrestrial non-target plants.

Birds: Tolpyralate was not toxic to birds on an acute oral or dietary basis. No treatment related effects were observed in bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*). For zebra finch (*Taeniopygia guttata*), there was one mortality (albeit with no definitive cause) in the highest test concentration under acute oral exposure conditions. No other mortalities and no other treatment related effects were observed in the zebra finch. The RQ for birds resulting from acute oral or dietary exposure to tolpyralate did not exceed the LOC at the screening level.

Following chronic exposure to tolpyralate, reproduction of bobwhite quail and mallard duck were affected at a concentration of 47.8 mg a.i./kg diet (equivalent to 5 mg a.i./kg bw/day; reduced number of eggs laid) and 102 mg a.i./kg diet (equivalent to 14.2 mg a.i./kg bw/day; reduced number of hatchlings), respectively. The screening level reproductive RQ for birds did not exceed the LOC. The summary of the screening level risk assessment to birds is presented in Appendix I, Table 16.

Mammals: The toxicity of tolpyralate to rats was used to determine the risk to small terrestrial mammals. No adverse effects were reported when rats were exposed to tolpyralate on an acute basis. The RQ for mammals resulting from acute exposure to tolpyralate did not exceed the LOC at the screening level.

The multigenerational dietary reproductive exposure of tolpyralate to rats resulted in an increased loss of offspring and a reduction in bodyweight of offspring. The NOEL and LOEL were determined to be 3.57 and 71.4 mg/kg bw/d, respectively. The RQ calculated with the NOEL resulting from the dietary reproductive exposure marginally exceeded the LOC (RQ of 1.4 for medium sized mammals) at the screening level only for medium sized mammals (Appendix I, Table 17). The screening level risk assessment for reproduction for medium sized mammals was, therefore, expanded to include all feeding guilds and exposure levels, as well as both on- and off-field exposure scenarios. This is presented in Appendix I, Table 18. Results from this assessment suggest a relatively low likelihood that adverse effects on mammal reproduction would be observed from the use of tolpyralate. The RQs only marginally exceeded the LOC with maximum on-field residue values for medium sized herbivores (short grass (RQ of 1.40) and broadleaf plants (RQ of 1.30)). When using the LOEL, the resulting RQ values (not shown here) are all well below the LOC for the medium sized herbivores. This indicates that concentrations of tolpyralate in the environment following its application would not reach levels at which adverse effects on mammal reproduction was observed under laboratory conditions. Based on the overall results, the risk to small mammals is anticipated to be low.

4.2.2 Risks to Aquatic Organisms

A risk assessment of tolpyralate, its transformation product, MT-2153, and one formulated product, SL-573 400SC, was conducted for freshwater and marine aquatic organisms based on available toxicity data.

For acute toxicity studies, uncertainty factors of ½ and 1/10 the EC_{50} (LC_{50}) are typically used for aquatic plants and invertebrates, and fish species, respectively, when calculating RQs. No uncertainty factors are applied to chronic NOEC endpoints. For groups where the LOC is exceeded (i.e. RQ≥1), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift and runoff separately. RQs for tolpyralate and its transformation products were calculated based on the highest maximum seasonal application rate for all uses. The screening level RQs for tolpyralate and its transformation product, MT-2153 are summarized in Appendix I, Tables 19 and 20, respectively.

A summary of the toxicity data to non-target organisms is presented in Appendix I, Table 12.

Freshwater invertebrates: No adverse effects were observed when daphnids were exposed to either tolpyralate, MT-2153, or a tolpyralate formulated product, SL-573 400SC, on an acute and chronic basis. The acute and chronic RQs for daphnids did not exceed the LOC at the screening level.

Freshwater fish and amphibians: The toxicity of tolpyralate to three freshwater species of fish was assessed for acute exposure (rainbow trout, fathead minnow and common carp) while toxicity from chronic exposure (early life-stage) was assessed on fathead minnow. The acute toxicity of MT-2153 and the tolpyralate formulated product, SL-573 400SC, was also assessed on the rainbow trout. No adverse effects were observed in any of the above mentioned acute or chronic studies to the rainbow trout, fathead minnow and common carp.

The risk to aquatic life stages of amphibians was assessed using fish toxicity values as surrogate endpoints using EECs in 15 cm water depth.

The screening level RQs for freshwater fish and amphibians for both acute and chronic exposure to tolpyralate, MT-2153 and SL-573 400SC did not exceed the LOC.

Freshwater algae and vascular plants: Tolpyralate was found to reduce biomass (area under the curve) of freshwater nonvascular green alga (*Pseudokirchneriella subcapitata*) and freshwater diatom algal species (*Navicula pelliculosa*) on an acute basis and was found not to have any adverse effects to freshwater nonvascular cyanobacterium ("blue-green alga"; *Anabaena flos-aquae*) on an acute basis. The RQs for freshwater algae resulting from acute exposure to tolpyralate did not exceed the LOC at the screening level.

Exposure of tolpyralate and MT-2153 resulted in reduced dry weight based on yield in the freshwater vascular plant, duckweed, *Lemna gibba*. The RQs for freshwater vascular plants resulting from acute exposure to tolpyralate and MT-2153 exceeded the LOC at the screening level; the LOCs were 1.70 and 7.45 for tolpyralate and MT-2153, respectively. A refined Tier I

assessment based on over-land run-off of tolpyralate into a receiving water body was conducted for acute exposure for duckweed. The LOC was not exceeded for acute exposure of tolpyralate to duckweed but was still marginally exceeded for MT-2153 (RQ of 2.4) (Appendix I, Table 21).

Marine/estuarine species: Tolpyralate was acutely toxic to mysid shrimp (*Americamysis bahia*), Eastern oyster (*Crassostrea virginica*) and marine diatom (*Skeletonema costatum*) but was not toxic to sheepshead minnow (*Cyprinodon variegatus*). The screening LOC was not exceeded for any marine/estuarine species tested.

5.0 Value

5.1 Consideration of Benefits

There are many alternatives for post-emergent weed control in field corn, including but not limited to the following active ingredients: halosulfuron, thiencarbazone-methyl, nicosulfuron, rimsulfuron, (Group 2); 2,4-D, dicamba, MCPA (Group 4); bromoxynil (Group 6); glyphosate (in glyphosate tolerant field corn, Group 9); glufosinate ammonium (in glufosinate ammonium tolerant field corn, Group 10); dimethenamid, pyroxasulfone, s-metolachlor (Group 15); diflufenzopyr (Group 19); mesotrione, tembotrione, topramezone (Group 27).

Alternative herbicides in sweet corn, seed corn and popcorn are more limited in number and mode of action but include many of the same active ingredients for field corn.

Tolpyralate 400SC Herbicide provides an option of using a Group 27 mode of action herbicide with a low rate of atrazine for weed control in all types of corn. An application of Tolpyralate 400SC Herbicide in tank mix with atrazine offers control or suppression of select emerged broadleaf and grassy weeds in corn (field, sweet, seed and pop). It is compatible with integrated weed management practices and with both conservation tillage and conventional tillage systems.

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of selecting for naturally resistant biotypes. Several broadleaf and grassy weed species have been documented throughout Canada to have biotypes that are resistant to one or more herbicide modes of action. This includes Weed Science Society of America Group 2 (acetolactate synthase inhibitors), Group 4 (synthetic auxins), Group 5 (inhibitors of photosynthesis at photosystem II), Group 7 (inhibitors of photosynthesis at photosystem II), Group 9 (EPSP synthase inhibitors), and Group 22 (photosystem I electron diversion).

When applied at the labelled use rate, Tolpyralate 400SC Herbicide may control or suppress biotypes of labelled weeds that are resistant to other groups of chemistries. Consequently, tolpyralate has the potential to delay the onset of herbicide resistance and to combat certain forms of resistance once present, by means of tank mixing and/or rotation with herbicides of other modes of action.

The label of Tolpyralate 400SC Herbicide includes the resistance management statements, as per Regulatory Directive DIR2013-04, *Pesticide Resistance Management Labeling Based on Target Site Mode of Action.*

5.2 Effectiveness Against Pests

The data from 140 small plot field trials conducted in Canada (BC, MB and ON) and the United States (northern and mid-western states) where growing conditions are similar to those in Canadian corn growing regions established the efficacy of Tolpyralate 400SC Herbicide alone at different rates. The data indicate that Tolpyralate 400SC Herbicide suppresses or controls labelled weeds when applied according to the directions for use. These data also demonstrated that when Tolpyralate 400SC Herbicide is tank mixed with atrazine, within the lower range of the approved registered use rate for atrazine, control of labelled weeds is improved.

5.3 Non-Safety Adverse Effects

As demonstrated in 140 small scale trials, field corn, seed corn, sweet corn, and popcorn all have acceptable tolerance to tolpyralate, even at exaggerated application rates. To mitigate potential variation in crop response, there is a warning statement on the label that not all corn inbred lines have been tested for tolerance to tolpyralate.

With regards to rotational cropping intervals, the data from 23 field trials support rotational cropping intervals ranging from immediate plantback to 18 months. Refer to Appendix I, Table 22 for more details.

5.4 Supported Uses

The value information in the form of data from small plot field trials was sufficient to support the claims for Tolpyralate 400SC Herbicide. Details of the supported uses are provided in Appendix I, Table 22.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, tolpyralate and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

> Tolpyralate does not meet the Track 1 criteria and will not form any transformation products which meet the Track 1 criteria. See Table 23 for comparison with Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

> Technical grade tolpyralate and the end-use product Tolpyralate 400SC Herbicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for tolpyralate is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in mice after longer-term dosing. Eye tumours were noted in rats; however, although qualitatively relevant, they were not considered quantitatively relevant to human risk assessment. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies as the developmental effects and total litter losses/pup survival occurred in the presence of maternal toxicity. In short-term and chronic studies on laboratory animals, the primary targets were body weight, the liver, kidney, pancreas, neural tissue and thyroid. The risk assessment

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders and applicators handling Tolpyralate 400SC Herbicide and workers re-entering treated corn fields are not expected to be exposed to levels of tolpyralate that will result in health risks of concern when Tolpyralate 400SC Herbicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants (maize) and animals is adequately understood. The residue definition for enforcement is tolpyralate in corn and tolpyralate and the metabolite MT-2153 in animal matrices. The proposed use of tolpyralate on field corn (including seed corn), sweet corn and popcorn does not constitute a health risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of tolpyralate.

Commodity	Recommended MRL (ppm)
Field corn, popcorn grain, sweet corn kernels plus cob with husks removed	0.01
Eggs; fat, meat and meat byproducts of cattle, goat, hog, horse, poultry and sheep; milk	0.02

7.2 Environmental Risk

Tolpyralate is rapidly transformed in the terrestrial environment to form several major transformation products of which only MT-2153 was observed in more than one environmental compartment. MT-2153 is more persistent than tolpyralate in the terrestrial environment. Large amounts of transformation products resulting from microbial degradation are also formed as unextracted residues in the terrestrial environment. Based on the field studies, the criteria of Cohen *et al.* and the groundwater ubiquity score (GUS); tolpyralate is not expected to leach into ground water. Although MT-2153 was not detected below the plough layer in field studies, all other criteria suggest that MT-2153 may have the potential to leach into ground water.

In aquatic systems, tolpyralate is rapidly transformed to form one major transformation product, MT-2153. High amounts of unextractable residues are also observed in water/soil systems. Similar to the terrestrial environment, MT-2153 is persistent in aquatic systems.

Tolpyralate is not expected to bioconcentrate or bioaccumulate in aquatic systems.

Tolpyralate does not pose a risk to most non-target aquatic organisms, but may post a risk to non-target aquatic vascular plants. Tolpyralate is unlikely to be consumed in sufficient quantities from feed items to cause adverse effects to small wild mammals. The use of tolpyralate may pose a risk to terrestrial vascular plants. Label statements are required on tolpyralate end-use products to inform users of this potential risk.

7.3 Value

There are several Group 27 herbicides registered for application post-emergence in corn for control of emerged weeds. The value of Tolpyralate 400SC Herbicide relates to its effectiveness against pests in tank mix with a low rate of atrazine, and potential contribution to herbicide resistance management as well as providing growers an additional weed control option within the Group 27 mode of action category, particularly for sweet, seed and popcorn that have fewer registered herbicide options.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of Technical Tolpyralate Herbicide and Tolpyralate 400SC Herbicide, containing the technical grade active ingredient tolpyralate, for post-emergent weed control in field corn (including corn grown for seed), sweet corn and popcorn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂	male
♀	females
<	less than
>	greater than
µg	micrograms
λ	wavelength
A	Applicator
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
AMS	ammonium sulfate
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
ATPD	area treated per day
BAF	Bioaccumulation Factor
BBCH	growth development stages for cereals
BC	British Columbia
BCF	Bioconcentration Factor
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAM	chemical application method
CAS	Chemical Abstracts Service
CEC	cation exchange capacity
chol	cholesterol
CI	lower and upper confidence level of HC_5
clin	clinical
cm	centimetres
CO_2	carbon dioxide
CR	chemical resistant
d	day
DACO	data code
DAT	days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model
DFOP	double first order in parallel
DFR	dislodgeable foliar residue
DIR	Directive
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)

DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ER_{50}	effective rate on 50% of the population
equiv	equivalent
EP	end-use product
EPSP	5-encopyruvylshikimate-3-phosphate synthase
F1	first generation
F2	second generation
FA	fraction of species affected
fc	food consumption
FDA	*Food and Drugs Act*
fe	food efficiency
FIR	food ingestion rate
g	gram(s)
GAP	good agricultural practices
GD	gestation day
gen. pop	general population
G.I.	gastrointestinal
ha	hectare(s)
HAFT	highest average field trial
HC_5	hazardous concentration to 5% of the species
HCl	hydrochloric acid
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPPD	4-hydroxyphenylpyruvate dioxygenase
HRAC	Herbicide Resistance Action Committee
h	hour(s)
IC_{50}	inhibition concentration 50%
ID	identity
IL	Illinois
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_d	soil-water partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LC-MS	liquid chromatography with mass spectrometry
LD	lactation day
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level

LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting
m	metre(s)
M	moles/L
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score for 24, 48 and 72 hours
MB	Manitoba
MCH	Mean corpuscular haemoglobin
M/L/A	Mixer/Loader/Applicator
MO	Missouri
MOE	margin of exposure
mol	mole
MRID	United States Master Record Identification Number
MRL	maximum residue limit
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MSO	methylated seed oil
MW	molecular weight
N	North
N/A	not applicable
NC	North Carolina
ND	North Dakota
ND	not detected
NAFTA	North American Free Trade Agreement
NaOH	Sodium Hydroxide
nec	necropsy
nm	nanometre
nmol	nanomoles
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NTBC	2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione
NOER	no observed effect rate
NY	New York
NZW	New Zealand white
OC	organic carbon
ON	Ontario
P	parental generation
Pa	Pascal
PBI	plantback interval
PFC	Plaque Forming Cell Assay
pH	measure of the acidity or basicity of an aqueous solution
PHI	preharvest interval
p*K*a	dissociation constant

PMRA	Pest Management Regulatory Agency
PPE	Personal protective equipment
PEI	Prince Edward Island
ppm	parts per million
PWC	Pesticide in Water Calculator
QC	Quebec
r^2	calculated dissipation equation
RASP	raspberry
RD	residue definition
REI	Restricted entry interval
rel	relative
RQ	risk quotient
SC	soluble concentrate
SD	standard deviation
SE	seedling emergence
SFO	single order
SMILES	simplified molecular input line entry system
SPF	specific-pathogen-free
SSD	species sensitivity distribution
$t_{1/2}$	half-life
t_R	representative degradation half-life
TAT	tyrosine aminotransferase
TC	Transfer coefficient
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UK	United Kingdom
USA	United States of America
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
V	vegetative
vs	versus
VV	vegetative vigor
WSSA	Weed Science Society of America (WSSA)
wt	weight
wts	weights

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference PMRA #
Soil		tolpyralate / SL-573	HPLC/MS-MS	1 µg/kg		2522685, 2522684, 2522686, 2581982
		MT-2153		1 µg/kg		
		MMTA		1 µg/kg		
Water		tolpyralate / SL-573	HPLC/MS-MS	0.01 µg/L		2522688, 2522689
		MT-2153		0.01 µg/L		
Plant	JSM0433	Tolpyralate and MT-2153	HPLC-MS/MS	0.01ppm /analyte	Maize commodities (grain, forage, stover), lettuce, oilseed rape seeds and grapes	2522682, 2522847, 2522681
Animal	D96518	Tolpyralate and MT-2153	HPLC-MS/MS	0.01ppm /analyte	Eggs, bovine liver, kidney, milk, meat and fat	2522683, 2581919

Table 2 Metabolite Identification

Metabolite Identifier	Chemical name
MMTA	3-(2-methoxyethoxy)-2-methyl-4-(methylsulfonyl)benzoic acid
MT-2153	(1-ethyl-5-hydroxy-1H-pyrazol-4-yl)(3-(2-methozyethoxy)-4-mesyl-2-methylphenyl)
TAT-834	(1-ethyl-5-hydroxy-1H-pyrazol-4-yl)(3-(2-methozyethoxy)-2-methyl-4-(methylsulfonyl)phenyl)methanone

Table 3 Toxicity Profile of Tolpyralate 400SC Herbicide

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Crl:CD® (SD) rats PMRA 2522990	LD_{50} > 2000 mg/kg bw Low Toxicity
Acute Dermal Toxicity Crl:CD® (SD) rats PMRA 2522991	LD_{50} > 2000 mg/kg bw Low Toxicity

Study Type/Animal/PMRA #	Study Results
Acute Inhalation Toxicity Crl:CD® (SD) rats PMRA 2522992	LC_{50} > 2.74 mg/L Low Toxicity
Eye Irritation New Zealand White rabbits (Kbl:NZW) PMRA 2522994	MAS (24-72 hours) = 0/110 Non-irritating
Skin Irritation New Zealand White rabbits (Kbl:NZW) PMRA 2522993	MAS (24-72) = 0/8 Non-irritating
Dermal Sensitization – LLNA CBA/J mice PMRA 2522996	Not a dermal sensitizer
Dermal Sensitization –Buehler Hartley albino guinea pig PMRA 2522995	Not a dermal sensitizer

Table 4 Toxicity Profile of Technical Tolpyralate

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Metabolism Crl:WI (Han) rats PMRA 2522692; 2522693; 2922694; 2922695; 2620665	Metabolism was investigated with phenyl- and pyrazole-labelled tolpyralate in single doses at 3 and 200 mg/kg bw and repeat doses at 3 mg/kg bw/day for 15 days. Tolpyralate was quickly and extensively absorbed (75-85%) and rapidly excreted. There were few differences between sexes, doses or label positions. There was no evidence of saturation of the metabolic pathways. Tissue concentrations after 96 hours were less than 5% of the administered dose and the highest concentrations were in the G.I. tract, liver, kidney and carcass, though measurable amounts were found in the muscle. Excretion was primarily via the urine (38 – 61%), with faecal excretion divided more or less evenly between unabsorbed compound and bile. Elimination was between 91 – 103% by 96 hours. The proposed metabolic pathway was dealkylation and subsequent conjugation with glucuronic acid. The absorbed active is completely metabolised and the major metabolites were TAT-834 and MT-2153 with MMTA present before being quickly broken down. The liver metabolism is similar in the mouse, rat and human microsomes.

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Crl:CD® (SD) rats PMRA 2522697	LD_{50} > 2000 mg/kg bw Low Toxicity
Acute Dermal Toxicity Crl:CD® (SD) rats PMRA 2522700	LD_{50} > 2000 mg/kg bw Low Toxicity
Acute Inhalation Toxicity Crl:CD® (SD) rats PMRA 2522701	LC_{50} > 2.01 mg/L Low Toxicity
Eye Irritation New Zealand White rabbits (Kbl:NZW) PMRA 2522703	MAS (24-72 hours) = 0/110 Non-irritating
Skin Irritation New Zealand White rabbits (Kbl:NZW) PMRA 2522702	MAS (24-72 hours) = 0/8 Non-irritating
Dermal Sensitization – LLNA CBA/J mice PMRA 2522704	Not a dermal sensitizer
Dermal Sensitization – Maximization Hartley albino guinea pig PMRA 2522705	Not a dermal sensitizer
Short-term toxicity	
14-day dietary toxicity HRA Beagle PMRA 2522711 Palatability and range-finding	NOAEL and LOAEL were not established as the study was considered supplemental No adverse effects were observed up to 828 mg/kg bw/day, the highest dose tested.

Study Type/Animal/PMRA #	Study Results
28-day dietary toxicity study (SPF) Wistar Hannover rats PMRA 2522706 Range-finding	NOAEL and LOAEL were not established as the study was considered supplemental ≥ 4.5/5.0 mg/kg bw/day: ↑ eye opacity ♂♀; ↑ thyroid follicular cell hypertrophy, hyaline droplet deposition, ↑ eye keratitis ♂ ≥ 46/47 mg/kg bw/day: ↑ liver wts ♂♀; ↑ eye keratitis, ↑ triglycerides ♀ ≥ 447/496 mg/kg bw/day: ↑ triglycerides, chol, ↑ relative kidney wts, ↑ pancreatic single cell acinar cell necrosis ♂ 1799/1907 mg/kg bw/day: ↓ bw, ↑ pancreatic single cell acinar cell necrosis ♀
28-day dermal toxicity study Crl:CD® (SD) rats PMRA 2522717	Systemic NOAEL: undetermined Systemic LOAEL: > 1000 mg/kg bw/day Signs of irritation: ≥ 300 mg/kg bw/day: dequamation (D3-10), erythema ♂♀
90-day dietary toxicity study ICR [Crlj:CD1(ICR)] mice PMRA 2522710	NOAEL = 284/331 mg/kg bw/day LOAEL = 1056/1176 mg/kg bw/day Effects at the LOAEL: ↑ renal tubule basophilic change ♂♀; ↑ centrilobular hepatocyte vacuolation ♂; ↑ hepatocellular hypertrophy, focal hepatocyte necrosis and single cell hepatocyte necrosis ♀
90-day dietary toxicity study (SPF) Wistar Hannover rats PMRA 2522709	NOAEL = 1.3/1.6 mg/kg bw/day LOAEL = 113/159 mg/kg bw/day Effects at the LOAEL: ↑ eye opacity, neovascularization, keratitis, ↓ pupillary reflex, ↑ urinary ketones, ↑ thyroid follicular cell hypertrophy ♂♀; ↑ chol, ↓ urinary pH, ↑ liver and kidney wts, ↑ acinar single cell in pancreas ♂; ↑ triglycerides ♀
28-day dietary toxicity study HRA Beagle PMRA 2522714 Range-finding study	NOAEL and LOAEL were not established as the study was considered supplemental ≥ 69/72 mg/kg bw/day: ↑ urinary ketones 709/711 mg/kg bw/day: ↑ tubular regeneration and urinary casts ♂♀; ↓ bw ♂
90-day dietary toxicity study HRA Beagle PMRA 2522713	NOAEL = 65/65 mg/kg bw/day LOAEL = 699/671 mg/kg bw/day Effects at the LOAEL: ↓ bw, fe ♂; opacity, keratitis of eye ♀
1-year dietary toxicity study HRA Beagle PMRA 2522715	NOAEL = 28/29 mg/kg bw/day LOAEL = 321/295 mg/kg bw/day Effects at the LOAEL: ↓ bw and fe, conjunctival edema and congestion, abnormal stool, ↑ fibrinogens, ↓ MCH, ↑ liver wts, ↑ inflammatory cells of sinus of liver, ↑ granulopoeisis of bone marrow with ↑ neutrophils, ↑ mild hyperplasia of interior iliac lymph nodes ♂; ↑ ALP ♀
Long-term and carcinogenicity studies	
18-month dietary carcinogenicity study ICR [Crlj:CD1(ICR)] mice PMRA 2522724	NOAEL – Not established LOAEL = 7.4/7.2 mg/kg bw/day Effects at the LOAEL: ↑ calculi of the gallbladder ♂♀; ↑ tactile hair loss ♀

Study Type/Animal/PMRA #	Study Results
1-year dietary chronic toxicity study Wistar Hannover GALAS rats PMRA 2522722	NOAEL = 0.92/1.2 mg/kg bw/day LOAEL = 97/126 mg/kg bw/day Effects at the LOAEL: ↑ loss of fur, ↑ eye opacity (clin, ophthalmoscopy/gross ♂♀) and neovascularization ♂♀, ↑ urinary ketones, ↓ urinary pH, ↑ rel liver wts, ↑ loss of fur at gross nec, thyroid follicular cell hypertrophy, keratitis of eye ♂♀; ↓ bw, fc, ↑ urinary specific gravity, ↑ abs liver wts, ↑ kidney wts, ↑ centrilobular hepatocyte fatty change, ↑ acinar cell atrophy/fibrosis and necrosis, ↑ renal tubule basophilic change, ↑ molecular layer vacuolation in cerebellum ♂; soiled fur, wetted fur ♀
2-year dietary carcinogenicity study Wistar Hannover GALAS rats PMRA 2522723	NOAEL = 0.78/1.0 mg/kg bw/day LOAEL = 84/108 mg/kg bw/day Effects at the LOAEL: ↑ tactile hair loss, loss of fur, soiled fur and wetted fur, eye opacity (clin and gross nec), callouses on extremities, ↑ rel liver wts, vacuolation of molecular layer in cerebellum, degeneration of sciatic nerve fibre, pancreatic acinar cell atrophy/fibrosis, colloid degeneration of thyroid, keratitis of eye ♂♀; ↓ brain wts, ↑ masses and cysts on eye, ↓ bw, ↑ rel kidney wts, ↑ coarse surface and cysts of kidneys, ↑ eye masses at gross nec, squamous cell carcinomas in eye ♂; ↑ chronic nephropathy ♀
Developmental/Reproductive Toxicity Studies	
Dietary reproductive toxicity study Crl:CD® (SD) rats PMRA 2522727 Range-finding	NOAEL and LOAEL were not established as the study was considered supplemental Parental toxicity: ≥ 0.3/0.3 mg/kg bw/day: ↓ bwg premating/mating ♂ ≥ 12/13 mg/kg bw/day: ↑ eye opacity ♂♀; ↓ bw mating, ↑ rel liver wt ♂ ≥ 119/137 mg/kg bw/day: ↑ eye opacity at gross pathology ♂♀; ↑ abs liver wt, ↑ kidney and thyroid wts ♂; ↓ bwg premating /lactation, ↓ fc lactation, ↓ fertility ♀ 1196/1405 mg/kg bw/day: ↓ bw premating ♂; ↑ liver, kidney and thyroid wts ♀ Reproductive toxicity: 1196/1405 mg/kg bw/day: ↓ live birth index, ↑ pups found dead LD 0 Offspring toxicity: ≥ 12/13 mg/kg bw/day: ↑ pelvic dilatation ≥ 119/137 mg/kg bw/day: ↑ lost pups LD 1 – 4, ↓ pup bw, ↑ pale kidneys 1196/1405 mg/kg bw/day: ↓ viability index, ↑ lost/found dead LD 5 – 21, ↑ small pups, ↑ eye opacity (clin and gross)

Study Type/Animal/PMRA #	Study Results
Dietary reproductive toxicity study Crl:CD® (SD) rats PMRA 2522726	Parental NOAEL = 0.3/0.3 mg/kg bw/day Parental LOAEL = 3.1/3.5 mg/kg bw/day Effects at the parental LOAEL: ↑ kidney nephropathy F1 ♂ Reproductive NOAEL = 3.5 mg/kg bw/day ♀ / 61 mg/kg bw/day ♂ Reproductive LOAEL = 71 mg/kg bw/day ♀ / undetermined ♂ Effects at the reproductive LOAEL: ↑ # days to mating P/ F1, ↓ viability day 0 P/F1, ↓ gestation index F1, ↓ females with normal estrous cycles Offspring NOAEL = 3.5 mg/kg bw/day Offspring LOAEL = 71 mg/kg bw/day Effects at the offspring LOAEL: ↑ pups lost LD 1-4, 8-14 F1, ↑ pups killed in extremis D8-14 F2, ↓ bw d 14 -21 F1/F2, ↑ pale kidneys, pelvic dilation, cysts, small kidneys F1/F2, ↑ interocular haemorrhages F1, ↑ eye opacity F2, ↑ age to sexual maturity ♂♀
Rat gavage teratology study Crl:CD® (SD) rats PMRA 2522728 Range-finding	NOAEL and LOAEL were not established as the study was considered supplemental Maternal: ≥ 100 mg/kg bw/day: ↓ bwg, ↓ fc GD 6 – 9, 12 - 15 1000 mg/kg bw/day: ↓ gravid uterine wts, ↓ fc GD 6 – 15, ↑ % resorptions, % early resorptions, resorptions/dam, early resorptions/dam Developmental: 1000 mg/kg bw/day: ↓ live fetuses and live fetuses/dam, ↑ % resorptions, % early resorptions, resorptions/dam, early resorptions/dam, post-implantation loss, ↑ placental wts, ↑ skeletal variations, ↑ supernumerary ribs
Rat gavage teratology study Crl:CD® (SD) rats PMRA 2522731	Maternal NOAEL = 10 mg/kg bw/day Maternal LOAEL = 500 mg/kg bw/day Effects at the maternal LOAEL: ↑ red sebum, ↓ bwg especially in first 3 days of treatment, ↓ fc GD 6 – 12 Developmental NOAEL = 10 mg/kg bw/day Developmental LOAEL = 500 mg/kg bw/day Effects at the developmental LOAEL: ↓ fetal wts, ↑ fetuses with variations (↑ branched rib cartilage, 27 presacral vertebrae)
Rabbit gavage teratology study Japanese White rabbits PMRA 2522732 Range-finding	NOAEL and LOAEL were not established as the study was considered supplemental Maternal toxicity: No adverse effects were observed up to the highest dose tested of 500 mg/kg bw/day. Developmental toxicity: 500 mg/kg bw/day: ↓ fetal bw, ↑ skeletal variations, 27 presacral vertebrae, supernumerary ribs

Study Type/Animal/PMRA #	Study Results
Rabbit gavage teratology study Japanese White rabbits PMRA 2522733	Maternal NOAEL = 5 mg/kg bw/day Maternal LOAEL = 500 mg/kg bw/day Effects at the maternal LOAEL: ↑ litters with total resorptions Developmental NOAEL = 5 mg/kg bw/day Developmental LOAEL = 500 mg/kg bw/day Effects at the developmental LOAEL: ↑ skeletal variations, supernumerary ribs, unossified 1st cervical centra, supernumerary ossification sites between 1st and 2nd cervical vertebrae, 27 presacral vertebrae, ↑ litters with total resorptions; ↓ fetal bw ♂
Genotoxicity Studies	
Bacterial Reverse Mutation Assay *Salmonella typhimurium* and *Escherichia coli* PMRA 2522718	Negative
In Vitro Mammalian Cell Assay Mouse Lymphoma L5178Y Cells PMRA 2522720	Positive @ cytotoxic and precipitating concentrations
Chromosome Aberration Assay Chinese Hamster CHL/IU (lung) Cells PMRA 2522719	Negative
In vivo Cytogenetics ICR (Crlj:CD1) ♂mice PMRA 2522721	Negative
Comet Assay Wistar Hannover GALAS rats PMRA 2522725	Negative
Neurotoxicity Studies	
Acute neurotoxicity gavage study S-D Rats PMRA 2522734	NOAEL = 1000 mg/kg bw/day LOAEL = 2000 mg/kg bw/day Effects at the LOAEL: ↓ bwg D 1- 8, ↓ rearing and activity Day 1 in open field ♂ No evidence of neurotoxicity

Study Type/Animal/PMRA #	Study Results
90-day dietary subchronic neurotoxicity study S-D Rats PMRA 2522735	Systemic NOAEL = 1.3/1.6 mg/kg bw/day Systemic LOAEL = 37.7/42.6 mg/kg bw/day Neurotoxicity NOAEL = 1041/1231 mg/kg bw/day Neurotoxicity LOAEL = undetermined Effects at the systemic LOAEL: opacity of eyes, stromal opacity with or without pigmentation and/or vascularisation, cornea: infiltration of inflammatory cells, ↑ failure of pupillary reflex secondary to opacity, epithelial hyperplasia, neovascularisation, endothelial vacuolation, erosion ♂♀; ↑ eye opacity at gross necropsy ♂
Special Studies	
Immunotoxicity Study CD-1 Mice (♀) PMRA 2522696 PFC Assay	NOAEL = 1002 mg/kg bw/day LOAEL = undetermined
Mode of Action Studies	
Rat Teratology Gavage Study in rats with tyrosinemia Crl:CD® (SD) rats PMRA 2581981	NOAEL and LOAEL were not established as the study was considered supplemental Maternal: L-tyrosine-supplemented diet: 1.8× control plasma tyrosine 0.1 mg/kg NTBC: ↓ bwg, 29.5× control plasma tyrosine, ↑ white corneal opacity, coarsened corneal surface, ↑ keratitis of eye 0.1mg/kg NTBC + L-tyrosine-supplemented diet :↑ eye opacity, ↓ bw/bwg, 46.8× control plasma tyrosine, white opacity, coarsened corneal surface, ↑ liver enlargement, ↑ rel liver wt, ↑ rel kidney wt, ↑ keratitis of eye, tubular basophilic change of the kidney, renal tubular dilatation, renal tubular necrosis Offspring: L-tyrosine-supplemented diet: 2.2× control plasma tyrosine, ↑ 14th ribs, ↑ dilatation of the urinary bladder 0.1 mg/kg NTBC: 8.6× control plasma tyrosine, ↑ kidney malformations/variations, ↑ dilatation of the urinary bladder, ↑ 14th ribs, ↑ supernumerary ribs, ↑ lumbosacral transitional vertebra, ↓ ossification 0.1mg/kg NTBC + L-tyrosine-supplemented diet: 11.2× control plasma tyrosine, ↓ fetal bw, ↑ kidney malformations/variations, ↑ supernumerary ribs, ↑ 14th rib, 27 presacral vertebrae, ↑ lumbosacral transitional vertebra, ↓ ossification
Measurement of plasma tyrosine following single dose Crl:CD® (SD) rats ♀ PMRA 2581978	NOAEL and LOAEL were not established as the study was considered supplemental 1000 mg/kg bw: ↑ plasma tyrosine at 1, 2, 4, 5, 8, 24, 28 and 72 hours with peak at 24 hours (26× control values)

Study Type/Animal/PMRA #	Study Results
Measurement of plasma tyrosine following single dose Japanese White (Kbl:JW) rabbits ♀ PMRA 2581979	NOAEL and LOAEL were not established as the study was considered supplemental 1000 mg/kg bw: ↑ plasma tyrosine at 1, 2, 4, 5, 8, 24, 28 and 72 hours with peak at 24 hours (20× control values)
Measurement of plasma tyrosine following single dose Crl:CD1(ICR) mice ♀ PMRA 2581980	NOAEL and LOAEL were not established as the study was considered supplemental 1000 mg/kg bw: ↑ plasma tyrosine at 1, 2, 4, 5, 8, 24, 28 and 72 hours with peak at 8 hours (13× control values)

Table 5 Toxicity Profile of Metabolites of Tolfenpyrad Technical

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/ Animal/ PMRA #	Study Results
MT-2153	
Acute oral toxicity study Crl:CD® (SD) rats PMRA 2522698	LD_{50} > 2000 mg/kg bw
Bacterial Reverse Mutation Assay *Salmonella typhimurium* and *Escherichia coli* PMRA 2522737	Negative
MMTA	
Acute oral toxicity study Crl:CD® (SD) rats PMRA	LD_{50} > 2000 mg/kg bw
Bacterial Reverse Mutation Assay *Salmonella typhimurium* and *Escherichia coli* PMRA 2522736	Negative

Study Type/ Animal/ PMRA #	Study Results
In Vitro Mammalian Cell Assay Mouse Lymphoma L5178Y Cells PMRA 2522738	Negative
Chromosome Aberration Assay Chinese Hamster CHL/IU (lung) Cells PMRA 2522739	Negative

Table 6 Toxicology Endpoints for Use in Health Risk Assessment for Tolpyralate

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Rat developmental toxicity study	Maternal NOAEL = 10 mg/kg bw Body weight loss from GD 6 - 9	100
	ARfD = 0.1 mg/kg bw		
Repeated dietary	Long-term rat study	NOAEL = 0.9 mg/kg bw/day Loss of fur, clinical signs of toxicity, liver, thyroid, pancreatic, kidney and neuropathological effects	100
	ADI = 0.009 mg/kg bw/day		
Short and Intermediate-term dermal and inhalation[2,3]	90-day rat oral toxicity study	NOAEL = 1.34 mg/kg bw/day	100
Cancer	Threshold approach was considered appropriate (ADI considered protective)		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2]Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 7 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN MAIZE	PMRA # 2522740, 2522741
Radiolabel Position	[^{14}C-Phenyl]-tolpyralate and [^{14}C-pyrazole]-tolpyralate
Test Site	Corn plants grown in plots in climate controlled greenhouse
Treatment	Foliar treatment
Total Rate	Low rate: 32-35 g a.i./ha; high rate: 80-117 g a.i./ha The test substance was applied in tank mix with Phase II adjuvant oil solution.
Formulation	Suspension concentrate (SC)
Samples at harvest	Forage from first immature harvest (BBCH51-65) Forage and ears from a second immature harvest (BBCH75-79) Kernels, cobs + foliage from mature harvest (BBCH87-89)

Harvest	Matrices	[^{14}C-Phenyl] TRRs (ppm)		[^{14}C-Pyrazole] TRRs (ppm)	
		Low Rate* (32-35 g a.i./ha)	High Rate (80-117 g a.i./ha)	Low Rate* (32-35 g a.i./ha)	High Rate (80-117 g a.i./ha)
First immature harvest	Whole plant	0.008	0.108	0.018	0.092
Second Immature	Foliage	0.013	0.025	0.011	0.012
	Ears	0.001	0.001*	0.001	0.001*
Third mature	Foliage plus cobs	0.019	0.038	0.015	0.052
	Kernels	0.001	0.002*	0.001	0.002*

*Due to low TRRs, residue characterization/identification was not conducted on these samples.

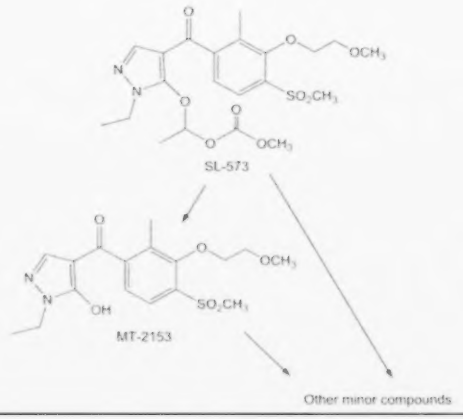
Total radioactive residues (TRRs) in all samples were determined using oxidation and liquid scintillation counting (LSC). The results of the initial estimation of TRRs in the commodities from the three harvests showed that residues were very low in both the low (0.001-0.019 ppm; both labels) and high rate samples (0.001-0.092 ppm; both labels). Because of the generally low levels, all additional analyses were restricted to the high rate samples. Residues in ears (second immature harvest) and kernels (mature harvest) from the high rate samples were <0.01 ppm; as such, no further work was performed on these commodities.

The ratios of the two enantiomers of tolpyralate in both the applied material and the tested sample extracts ranged from 0.8 to 1.5 (mean 1.0), with all but one (low level sample) in the range 0.8 to 1.1. Therefore, the ratio of enantiomers of tolpyralate is unaffected by metabolism in maize plants.

Metabolism of tolpyralate in maize proceeds via side chain removal to yield the metabolite MT-2153, followed by further degradation to minor metabolites and bound residues. **The residue definition in maize is tolpyralate.**

Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	**[^{14}C-Phenyl]**	**[^{14}C-Pyrazole]**	**[^{14}C- Phenyl]**	**[^{14}C-Pyrazole]**
Whole Plant - first immature harvest	Tolpyralate	Tolpyralate	MT-2153	MT-2153
Foliage of second immature harvest	Tolpyralate	Tolpyralate	MT-2153	MT-2153
Foliage + cob – mature harvest	--	Tolpyralate	Tolpyralate, MT-2153	MT-2153

Proposed Metabolic Scheme in Plants



CONFINED ACCUMULATION IN ROTATIONAL CROPS – Wheat, radish, mustard greens	**PMRA #2523002**
Radiolabel Position	[^{14}C-Phenyl]-tolpyralate and [^{14}C-Pyrazole]-tolpyralate
Test site	Sandy loam soil in crates maintained in two different greenhouses.
Formulation	Suspension concentrate (SC)
Application rate and timing	Bare soil was treated at 102 g a.i./ha ([^{14}C-Ph]-label) and 104 g a.i./ha ([^{14}C-Pz]-label) g a.i./ha, and aged for 29, 119 and 364 days.

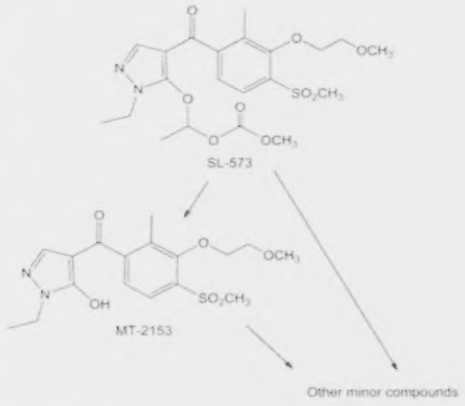
Individual extracts containing ≥ 0.01 ppm tolpyralate equivalents were further analysed by high performance liquid chromatography (HPLC) to quantify metabolites present. Maximum TRRs were 0.0505 ppm at 29 days after treatment (DAT) in the straw of wheat grown in soil treated with [^{14}C-Ph]-tolpyralate, 0.0741 ppm at 119 DAT PBI ([^{14}C-Pz] wheat straw) and 0.0451 ppm at 364 DAT PBI ([^{14}C-Ph] wheat hay). Levels were generally higher in soils treated with [^{14}C-Ph]-tolpyralate. TRR values in mustard greens ranged from 0.0006-0.0120 ppm. Lowest values were at the longest 364 DAT PBI and highest values at the 29 DAT PBI. Levels in immature harvests were generally lower than in mature harvests. TRR values in radishes ranged from 0.0012-0.0113 ppm. Levels were generally lower at the longest 364 DAT PBI than at the 29 DAT PBI.TRR values in wheat forage ranged from 0.0028-0.0164 ppm, values in hay ranged from 0.0198-0.0578 ppm, values in straw were between 0.0187-0.0741 ppm and values in grain ranged from 0.0029-0.0147 ppm.

MT-2153, polar material and unidentified metabolites were present in most samples analysed. Across all matrices tested, MT-2153 was detected at a maximum of 31% of the extracted TRRs (wheat forage, phenyl label; 0.0023 ppm, 29 DAT), but the highest actual concentration observed was <0.01 ppm (i.e., 0.0080 ppm; wheat straw, Ph-label; 11.8% extracted TRR, 119 DAT). Many samples contained three peaks of unidentified radioactivity, but there were no individual metabolites present at ≥0.01 ppm. Tolpyralate was not detected in any crop matrix, all PBIs.

Metabolites Identified		**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Matrices	**PBI (days)**	**[^{14}C- Phenyl]**	**[^{14}C-Pyrazole]**	**[^{14}C- Phenyl]**	**[^{14}C-Pyrazole]**
Wheat Forage	29	MT-2153	MT-2153	--	--
	119	Not analysed	Not analysed	--	Not analysed
	364	--		MT-2153	
Wheat Hay	29	--	MT-2153	MT-2153	--
	119	MT-2153	Not analysed	--	Not analysed
	364	--	MT-2153	MT-2153	--
Wheat Straw	29	MT-2153	MT-2153	--	--
	119	MT-2153	MT-2153	--	--
	364	--	MT-2153	MT-2153	Not analysed
Radish – mature foliage	29	MT-2153	MT-2153	--	--
Mustard Greens – mature foliage	29	--	--	MT-2153	MT-2153

Proposed Metabolic Scheme in Rotational Crops

Results from environmental behavior and fate studies indicate that when applied directly to aerobic soil, tolpyralate rapidly degrades via side chain removal to the metabolite MT-2153 with a DT_{50} of approximately < 1day in laboratory experiments, and 1-3 days in field dissipation trials. In both laboratory and field dissipation studies, the major metabolite in soil was MT-2153, which was formed rapidly at up to 79.0% on a molar basis under aerobic conditions and then declined, with a DT_{50} determined from field dissipation studies of between 28.7 and 76.1 days. Other metabolites were detected but did not account for more than 3.7% at any time. Combined with the confined rotational crop study, the metabolism of tolpyralate applied to soil proceeds rapidly and extensively via side chain removal to yield the metabolite MT-2153, which is subsequently taken up by rotational crops where it is further metabolized to minor unidentified metabolites.



NATURE OF THE RESIDUE IN LAYING HEN	**PMRA #2522742, 2611416**

Two groups of laying hens (five birds per treatment group) were dosed orally with [^{14}C]-tolpyralate at doses corresponding to 11.0-15.4 ppm ([^{14}C-Ph]-tolpyralate) and ~10.4-14.6 ppm ([^{14}C-Pz]-tolpyralate) in feed by gelatin capsule once daily for 14 days. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were euthanized 24 hours after administration of the final dose.

Matrices	**[^{14}C- Phenyl]**		**[^{14}C-Pyrazole]**	
	TRRs (ppm)	**% of Administered Dose [AD]**	**TRRs (ppm)**	**% of Administered Dose [AD]**
Excreta Total (Day 2 - 15)	--	99.7	--	93.4
Muscle (breast + leg + thigh)	0.0003	<0.01	0.002	<0.01
Fat	--	Not detected	0.0022	<0.01
Liver	1.378	0.33	1.418	0.34
Skin	0.0088	<0.01	0.007	<0.01
Eggs (whites + yolk, total day 2-15)	--	<0.01	--	<0.01

Absorption of [^{14}C]-tolpyralate was rapid, with detectable radioactivity in eggs collected on the afternoon following the first dose. Residues slowly increased in eggs, reaching a maximum steady state at approximately Day 12 of dosing (0.002984 mg equiv/kg ([^{14}C-Ph]-tolpyralate) and 0.004524 mg equiv/kg ([^{14}C-Pz]-tolpyralate). The majority of the administered dose (AD) was eliminated via excreta, with mean total recoveries of radioactivity of 99.7% ([^{14}C-Ph]-tolpyralate) and 93.4% ([^{14}C-Pz]-tolpyralate).

Tissue retention of radioactivity was low (~ 0.3% of the AD in liver) with <0.01% dose in all other tissues analysed. Tissue concentrations of radioactivity were highest in the liver (total radioactive residue [TRR] values of 1.378 ppm ([^{14}C-Ph]-tolpyralate) and 1.418 ppm ([^{14}C-Pz]-tolpyralate). Therefore, only liver was selected for further metabolite profiling work.

Metabolites MT-2153, MT-2650 and TAT-834 were identified in liver as the predominant residues. Specifically, TAT-834 and MT-2153 were major components and had the highest concentrations of 0.2713 ppm (19.7% of the TRR) and 0.7655 ppm (54% of the TRR), respectively. MT-2650 was a minor metabolite observed at lower levels, with a maximum concentration of 0.0260 ppm (1.8% of the TRR). A component designated L1 (0.1193 ppm; 8.7% of the TRR) was subsequently identified as MMTA. No glucuronide or sulfate conjugates were observed in organic extracts of liver. All other unknown components were present in liver at <6% of TRRs. Tolpyralate was not detected.

Metabolites identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-Phenyl]**	**[^{14}C-Pyrazole]**	**[^{14}C-Phenyl]**	**[^{14}C-Pyrazole]**
Liver	MT-2153, TAT-834	MT-2153, TAT-834	MT-2650, MMTA	MT-2650

NATURE OF THE RESIDUE IN LACTATING GOAT **PMRA #2522743**

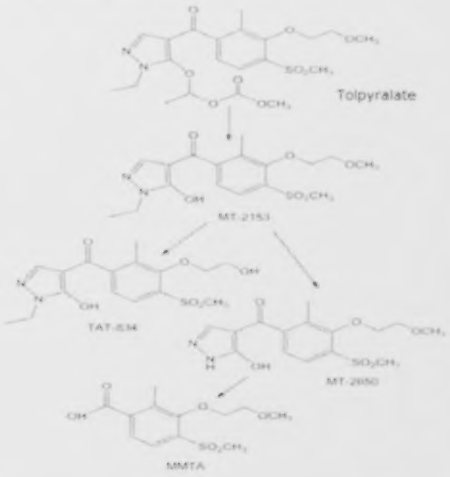
Two lactating goats were dosed orally with [^{14}C]-tolpyralate at doses corresponding to 19.5 ppm ([^{14}C-Ph]-tolpyralate) and 13.9 ppm ([^{14}C-Pz]-tolpyralate) in feed by gelatin capsule once daily for 7 days. Samples of excreta were collected daily and milk was collected twice daily. The goats were euthanized 23 hours after administration of the final dose.

Matrices	**[^{14}C-Phenyl]**		**[^{14}C-Pyrazole]**	
	TRRs (ppm)	**% of Administered Dose [AD]**	**TRRs (ppm)**	**% of Administered Dose [AD]**
Urine (Total Day 2-8)	--	75.74	--	76.54
Feces (Total Day 2-8)	--	11.60	--	15.33
Muscle (loin + flank)	Not detected	--	Not detected	--
Fat (renal + omental + subcutaneous)	--	<0.003	Not detected	--
Kidney	0.5119	0.072	0.4641	0.056
Liver	2.098	1.864	2.165	1.802
Milk (Total Day 1 – 8; aqueous + fat fractions)	--	<0.014	--	<0.009

Metabolites identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C-Phenyl]**	**[^{14}C-Pyrazole]**	**[^{14}C-Phenyl]**	**[^{14}C-Pyrazole]**
Liver	MT-2153	MT-2153	TAT-834	TAT-834
Kidney	MT-2153	MT-2153	TAT-834	Not detected

Proposed Metabolic Scheme in Livestock

Tolpyralate is primarily eliminated in the excreta (majority in the urine in goat). Significant residues were observed in kidney and/or liver only, where it is metabolized completely to the major metabolite MT-2153 via side chain removal. MT-2153 is further metabolized to TAT-834. No conjugates were observed.



FREEZER STORAGE STABILITY	PMRA #2523000

Plant matrices: Field corn forage and grain

The freezer storage stability data indicate that residues of tolpyralate and MT-2153 are stable at -15°C for 12 months.

CROP FIELD TRIALS & RESIDUE DECLINE ON FIELD CORN, SWEET CORN AND POPCORN	PMRA #2523001

Field trials on field corn, sweet corn and popcorn were conducted in 2013 in Canada and the United States. Trials were conducted in NAFTA Growing Regions 1, 2, 3, 5, 6, 7A, 10, 11, and 12 for a total of 20 field corn trials, 5 sweet corn trials and 3 popcorn trials. In addition, at 7 of the field corn trials, ears were harvested as well at the appropriate sweet corn growth stage, for a total of 12 sweet corn trials. SL-573 400SC, a soluble concentrate formulation was applied as a single foliar postemergent broadcast spray at 82-104 g a.i./ha (~1-1.3x -approved GAP) at growth stages V5-V9. No adjuvants were included in the spray solution. Decline studies for tolpyralate and the MT-2153 metabolite were conducted for field corn (2 sites), and sweet corn K+CWHR (1 site).Residue decline data show that residues of tolpyralate and MT-2153 decreased in field corn forage with increasing PHIs. Decline behaviour could not be assessed in field corn stover, grain and sweet corn as residues of tolpyralate or MT-2153 were non quantifiable at all PHIs tested.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	n	Residue Levels (ppm)				
				LAFT	HAFT	Median	Mean	SD
Tolpyralate								
Field corn forage	82-104	14-18	13	<0.01	0.021	0.010	0.011	0.003
		21-61	7	<0.01	<0.01	<0.01	<0.01	-
Field corn stover		85-122	20	<0.01	<0.01	<0.01	<0.01	-
Field corn grain			20	<0.01	<0.01	<0.01	<0.01	-
Sweet corn stage ears*	82-104	34-78	12	<0.01	<0.01	<0.01	<0.01	-
Popcorn	78-100	97-119	3	<0.01	<0.01	<0.01	<0.01	-
MT-2153								
Field corn forage	82-104	14-18	13	<0.01	0.012	0.010	0.010	0.0004
		21-61	7	<0.01	<0.01	<0.01	<0.01	-

Field corn stover		85-122	20	<0.01	<0.01	<0.01	<0.01	-
Field corn grain			20	<0.01	<0.01	<0.01	<0.01	-
Sweet corn stage ears*	82-104	34-78	12	<0.01	<0.01	<0.01	<0.01	-
Popcorn	78-100	97-119	3	<0.01	<0.01	<0.01	<0.01	-
* Includes field corn sampled at sweet corn stage (n = 7) and sweet corn ears (n = 5).								

RESIDUE DATA IN ROTATIONAL CROPS	**PMRA # --**
No data were provided and none are required given that tolpyralate residues in corn were <0.01 ppm in the confined rotational crop study at the 12-month PBI. The PBIs of 0 days for field corn, sweet corn and popcorn; 3 months for winter wheat and rye; 9 months for alfalfa; bean, dry; bean, green (including seed production); cabbage; canola, rapeseed; cotton; peas, field and edible; peanut; potato; rice; snap beans; sorghum; soybean; cucurbits; sunflower; tomato; spring wheat, barley, oats; 18 months for sugar beets; and, 12 months for all other rotational crops are acceptable.	

PROCESSED FOOD AND FEED - CROP	**PMRA #2523001**
Test Site	One trial in NAFTA Growing Region 6.
Treatment	A single broadcast foliar application at the V6 stage (vegetative).
Rate	503 g a.i./ha
End-use product/formulation	SL-573 400SC
Preharvest interval	111 days
Tolpyralate and MT-2153 residues were all <LOQ (<0.01 ppm) in bulk field corn grain and all processed commodities (i.e., flour, starch, oil, grits and meal). As such, processing factors could not be calculated for tolpyralate and MT-2153 in field corn grain processed fractions.	

LIVESTOCK FEEDING – Dairy cattle and laying hens	**PMRA # --**
Livestock and poultry feeding studies were not provided and are not required at this time given that no quantifiable transferable residues are anticipated in edible livestock/poultry commodities based on the anticipated dietary burdens.	

Table 8 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (corn)** **Rotational crops (wheat radish and mustard greens)**	Tolpyralate
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (corn)** **Rotational crops (wheat radish and mustard greens)**	Tolpyralate Tolpyralate (and MT-2153)* *For the domestic registration on corn, the proposed RD in rotational crops for dietary exposure purposes is "tolpyralate"; however, for future use expansions requiring supporting field accumulation data, analyses must be conducted for the metabolite MT-2153 in rotational crop matrices in the field accumulation study.
METABOLIC PROFILE IN DIVERSE CROPS	The profile in diverse crops cannot be determined, because only corn was investigated.
ANIMAL STUDIES	
ANIMALS	**Ruminant and Poultry**
RESIDUE DEFINITION FOR ENFORCEMENT	Tolpyralate and MT-2153
RESIDUE DEFINITION FOR RISK ASSESSMENT	Tolpyralate and MT-2153
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**	Is the profile similar in animals investigated? Yes

FAT SOLUBLE RESIDUE		Yes	
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
Basic chronic (cancer and non-cancer) dietary exposure analysis **ADI = 0.009 mg/kg bw/day** **Estimated chronic drinking water concentration = 37 µg a.i./L**	**All infants < 1 year**	3.3	34.4
	Children 1–2 years	11.0	22.4
	Children 3 to 5 years	6.6	15.9
	Children 6–12 years	3.7	10.7
	Youth 13–19 years	1.9	7.8
	Adults 20–49 years	1.4	9.6
	Adults 50+ years	1.2	9.2
	Females 13-49 years	1.4	9.5
	Total population	2.1	10.4
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Water**
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.1 mg/kg bw** **Estimated acute drinking water concentration = 37 µg a.i./L**	**All infants < 1 year**	1.3	7.0
	Children 1–2 years	2.1	4.0
	Children 3 to 5 years	1.2	2.9
	Children 6–12 years	0.8	2.2
	Youth 13–19 years	0.4	1.8
	Adults 20–49 years	0.3	2.1
	Adults 50+ years	0.3	1.8
	Females 13-49 years	0.3	2.1
	Total population	0.6	2.3

Table 9 Fate and behaviour of tolpyralate in the terrestrial environment

Study type	Test material/test system	Value	Transformation products	Comments	References
Abiotic transformation					
Hydrolysis	See Table 10 Fate and behaviour of tolpyralate in the aquatic environment				
Phototransformation on soil	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled 20°C; 15 d	Irradiated DT_{50} = 40.8 days (continuous irradiation) DT_{50} = 102.5 days (40°N latitude) Non-irradiated	Major: MT-2153, CO_2 Minor: none	Not a major route of dissipation	PMRA# 2522748 MRID# 49559457

Study type	Test material/test system	Value	Transformation products	Comments	References
	Test system: Sandy clay loam/sandy soil (Worcestershire, UK); pH 7.7; 4.4% OC; CEC 19.8	DT_{50} = 7.8 days			
Phototransformation in air	Tolpyralate is not expected to be volatile under field conditions based on vapour pressure (5.9×10^{-4} Pa at 25°C) and Henry's law constant (9.6×10^{-3} Pa·m^3·mol^{-1}) (1/H = 2.3×10^5). Transformation products of tolpyralate are not expected to be volatile under field conditions based on low detection of volatile organics in soil biotransformation studies. A phototransformation study in air is not required.				
Biotransformation					
Biotransformation in aerobic soil	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled 20°C; 120 d Test systems: a) IL01 (silty clay loam; Illinois, USA); pH 6.3; 2.4% OC; CEC 27.0 b) WA02 (loam; Washington, USA); pH 6.4; 0.9% OC; CEC 28.8 c) Evesham 3 (clay; Warwick, UK); pH 7.9; 4.0% OC; CEC 45.0 *Note, Evesham 3 soil was additionally incubated at 10°C	IL01 SL-573 DT_{50} = 0.5 days (SFO) DT_{90} = 1.6 days MT-2153 DT_{50} = 10.7 days (DFOP; Slow $t_{1/2}$ = 129 days) DT_{90} = 250 days WA02 SL-573 DT_{50} = 1.2 days (SFO) DT_{90} = 4.1 days MT-2153 DT_{50} = 16.3 days (DFOP; Slow $t_{1/2}$ = 116 days) DT_{90} = 260 days Evesham 3 (20°C) SL-573 DT_{50} = 0.04 days (IORE) DT_{90} = 0.4 days MT-2153 DT_{50} = 69.5 days (SFO) DT_{90} = 231 days Evesham 3 (10°C) SL-573 DT_{50} = 0.1 days (IORE) DT_{90} = 1.7 days MT-2153 DT_{50} = 84.8 days (SFO)	Major: MT-2153, MMTA (phenyl label), Ph-A, CO_2 Minor: Ph-B, Py-A, Py-B, Py-C	Major route of dissipation	PMRA# 2522746 MRID# 49580125

Study type	Test material/test system	Value	Transformation products	Comments	References
		DT_{50} = 282 days			
	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled 20°C; 120 d Test system: Elmton (sandy clay loam; Worcestershire, UK): pH 7.7; 4.4% OC; CEC 19.8	SL-573 DT_{50} = 0.1 days (IORE; $t_{R\ IORE}$ = 0.2 days) DT_{90} = 0.6 days MT-2153 DT_{50} = 112 days (DFOP; Slow $t_{1/2}$ = 255 days) DT_{90} = 701 days	Major: MT-2153, CO_2 Minor: Met A, Met B	Major route of dissipation	PMRA# 2522745 MRID# 49559458
	MMTA (major transformation product) Test system: Elmton (sandy clay loam); pH 8.0,; 3.3% OC; CEC 23.4	MMTA DT_{50} = 1.1 days DT_{90} = 3.6 days	No transformation producte were identified.	No transformation producte were identified.	PMRA# 2603352 MRID# 49815103
Biotransformation in anaerobic soil	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled 20°C; 120 d Test system: Elmton (sandy clay loam; Worcestershire, UK): pH 7.9; 3.9% OC; CEC 21.3	SL-573 DT_{50} = 0.02 days DT_{90} = 0.6 days MT-2153 DT_{50} = 245 days DT_{90} = 814 days	Major: MT-2153 Minor: none	Redox potentials in the water were indicative of an oxidizing aqueous phase, however, there was almost no oxyten in the ater. Redox potentials in the soil were generally negative, indicative of an anaerobic reducing soil phase. This does not adequately represent anaerobic soil conditions due to the fact that anaerobic conditions were never achieved in the water layer.	PMRA# 2522747 MRID# 49559459
Mobility					
Adsorption / desorption in soil	Tolpyralate (SL-573) Adsorption / desorption values were obtained in 5 soils: 4 UK soils and 1	HDRA Biogarden (sandy loam) K_d = 1.5 K_{OC} = 30.6 Cuckney (sand) K_d = 0.4 K_{OC} = 86.6	N/A	Tolpyralate is classified as having a high to very high potential for mobility in soil.	PMRA# 2522750 MRID# 49559462

Study type	Test material/test system	Value	Transformation products	Comments	References
	Japan soil. The test soils included a range of textural classes, with pH values (in $CaCl_2$) between 4.9 and 6.8 and organic carbon content between 0.5% and 5.0%.	Volcanic Ash (silt loam) K_d = 1.6 K_{OC} = 49.3 Fladbury (sandy clay loam) K_d = 0.5 K_{OC} = 15.2 Uttoxeter Quarry (clay) K_d = 1.7 K_{OC} = 41.1			
	MT-2153 (major transformation product) Adsorption / desorption values were obtained in 5 UK soils. The test soils included a range of textural classes, with pH values (in $CaCl_2$) between 4.80 and 6.21 and an organic carbon content between 0.37% and 3.8%.	Calke (sandy loam) K_d = 2.6 K_{OC} = 123.8 Cuckney (sand) K_d = 0.2 K_{OC} = 58.9 Fladbury (sandy clay loam) K_d = 1.6 K_{OC} = 58.6 HDRA Biogarden (sandy loam) K_d = 1.6 K_{OC} = 42.8 Uttoxeter Quarry (clay) K_d = 5.2 K_{OC} = 137.5	N/A	MT-2153 is classified as having a high to very high potential for mobility in soil.	PMRA# 2522751 MRID# 49580127
Volatilization	Not required due to low vapour pressure (5.9×10^{-1} Pa at 25°C) and Henry's law constant (9.6×10^{-3} Pa·m^3·mol^{-1}).				
Terrestrial Field studies					
Field dissipation of SL-573	Carlyle, IL	SL-573 DT_{50} = 6.1 days DT_{90} = 20.2 days MT-2153 DT_{50} = 0.7 days (IORE; $t_{R\ IORE}$ = 70.7 days) DT_{90} = 235 days	Major: MT-2153	SL-573 and MT-2153 residues were not observed below a depth of six inches (15.2 cm).	PMRA# 2523006 MRID# 49559467
	Northwood, ND	SL-573 DT_{50} = 2.8 days DT_{90} = 9.3 days	Major: MT-2153	SL-573 and MT-2153 residues were not observed below a	PMRA# 2523004 MRID#

Study type	Test material/test system	Value	Transformation products	Comments	References
		MT-2153 DT_{50} = 17.8 days (IORE; $t_{R\ IORE}$ = 63 days) DT_{90} = 209 days		depth of six inches (15.2 cm).	49559465
	North Rose, NY	SL-573 DT_{50} = 1.5 days DT_{90} = 5.0 days MT-2153 DT_{50} = 3.6 days (DFOP; slow $t_{½}$ = 56 days) DT_{90} = 108 days	Major: MT-2153	SL-573 and MT-2153 residues were not observed below a depth of six inches (15.2 cm).	PMRA# 2523009 MRID# 49559470
	Seven Springs, NC	SL-573 DT_{50} = 0.3 days (IORE; $t_{R\ IORE}$ = 0.9 days) DT_{90} = 3.0 days MT-2153 DT_{50} = 5.1 days (IORE; $t_{R\ IORE}$ = 17.9 days) DT_{90} = 59.4 days	Major: MT-2153	SL-573 and MT-2153 residues were not observed below a depth of three inches (7.6 cm).	PMRA# 2523003 MRID# 49559464

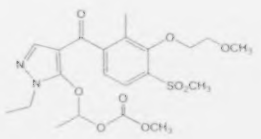
Table 10 Fate and behaviour of tolpyralate in the aquatic environment

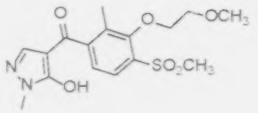
Study type	Test material/test system	Value	Transformation products	Comments	References
Abiotic transformation					
Hydrolysis	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled Test system: pH 4, 7 and 9; 10, 25 and 50°C	10°C pH 4: DT_{50} = 996 days pH 7: DT_{50} = 223 days pH 9: DT_{50} = 2.47 days 25°C pH 4: DT_{50} = 311 days pH 7: DT_{50} = 31.1 days pH 9: DT_{50} = 8.5 hours 50°C pH 4: DT_{50} = 25.9 days pH 7: DT_{50} = 1.84 days pH 9: DT_{50} = 0.7 hours	Major: MT-2153 Minor: none	Not a major route of dissipation	PMRA# 2522752 MRID# 49559455
	MT-2153	Stable to hydrolysys	None	Not a major route of	PMRA#

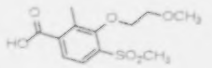
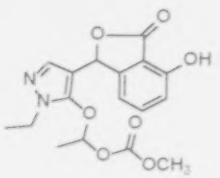
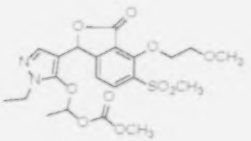
Study type	Test material/test system	Value	Transformation products	Comments	References
	(major transformation product)			dissipation	2603351 MRID# 49815102
Phototransformation in water	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled Test system: 25°C; natural and purified water; pH range of 5.3-6.7	Natural water DT_{50} = 5.2 days (continuous irradiation) DT_{50} = 18.6 days (40°N latitude) Purified water DT_{50} = 2.9 days (continuous irradiation) DT_{50} = 8.1 days (40°N latitude)	Major: MT-2153, EVC-005 (present as two isomeric forms), EVC-006 (present as two isomeric forms) Minor: CO_2	Not a major route of dissipation	PMRA# 2522753 MRID# 49559456 PMRA# 2522754 MRID# 49580142
Biotransformation					
Biotransformation in aerobic water systems	Tolpyralate (SL-573) [^{14}C-Ph] and [^{14}C-Pz] - labelled 20°C; 100 d Test systems: a) Swiss Lake (Derbyshire, UK) Water: 8.8 mg/L TOC; pH 5.8 Sediment: 0.8%OC; pH 6.3; CEC 4.2 b) Calwich Abbey Lake (Staffordshire, UK) Water: 2.9 mg/L TOC; pH 7.8 Sediment: 5.0%OC; pH 8.0, CEC 22.6	Swiss Lake SL-573; total system: DT_{50} = 1.8 days (SFO) DT_{90} = 5.9 days MT-2153; total system: DT_{50} = 190 days (SFO) DT_{90} = 631 days Calwich Abbey Lake SL-573; total system: DT_{50} = 1.4 days (SFO) DT_{90} = 4.6 days MT-2153; total system: DT_{50} = 225 days (SFO) DT_{90} = 747 days	Major: MT-2153 Minor: CO_2	Major route of dissipation	PMRA# 2522755 MRID# 49559460
Biotransformation in anaerobic water systems	Tolpyralate (SL-573) [^{14}C-Ph] and	Swiss Lake SL-573; total system: DT_{50} = 2.6 days (SFO)	Major: MT-2153 Minor: CO_2	Anaerobic conditions were not maintained in the water layer of both test systems. This	PMRA# 2522756 MRID# 49559461

Study type	Test material/test system	Value	Transformation products	Comments	References
	[^{14}C-Pz] - labelled 20°C; 100 d <u>Test systems:</u> a) Swiss Lake (Derbyshire, UK) Water: 6.6 mg/L TOC; pH 6.4 Sediment: 0.8%OC; pH 6.2; CEC 2.2 b) Calwich Abbey Lake (Staffordshire, UK) Water: 2.9 mg/L TOC; pH 8.0 Sediment: 5.2%OC; pH 8.0, CEC 16.4	DT_{90} = 8.7 days MT-2153; total system: DT_{50} = 491 days (SFO) DT_{90} = 1633 days <u>Calwich Abbey Lake</u> SL-573; total system: DT_{50} = 1.4 days (SFO) DT_{90} = 4.6 days MT-2153; total system: DT_{50} = 336 days (SFO) DT_{90} = 1118 days		does not adequately represent anaerobic aquatic conditions.	

Table 11 Tolpyralate and its transformation products.

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
PARENT							
Tolpyralate **SL-573**	**IUPAC:** 1-[2-ethyl-4-[3-(2-methoxyethoxy)-2-methyl-4-methylsulfonylbenzoyl]pyrazol-3-yl]oxyethyl methyl carbonate **CAS:** 1-[[1-ethyl-4-[3-(2-methoxyethoxy)-2-methyl-4-(methylsulfonyl)benzoyl]-1H-pyrazol-5-yl]oxy]ethyl methyl carbonate **CAS No.:** 1101132-67-5 **Formula:** $C_{21}H_{28}N_2O_9S$ **MW:** 484.52 g/mol **SMILES:** CCN1N=CC(C(=O)C2=C(C)C(OCCOC)=C(C=C2)S(C)(=O)=O)		Hydrolysis	2522758	pH 4, 10°C	99.3% (3 d)	97.3% (30 d)
					pH 7, 10°C	98.9% (1 d)	90.9% (30 d)
					pH 9, 10°C	98.2% (0 d)	13.8% (7 d)
					pH 4, 25°C	99.3% (1 d)	93.3% (30 d)
					pH 7, 25°C	98.3% (0 d)	50.6% (30 d)
					pH 9, 25°C	97.6% (0 d)	2.3% (2 d)
					pH 4, 50°C	99.1% (0 d)	44.7% (30 d)
					pH 7, 50°C	100.0% (0 d)	10.5% (30 d)
					pH 9, 50°C	98.0% (0 d)	ND (0.333 d)
			Aqueous photolysis	2522753	Purified water	92.6% (0 d) Irradiated 99.6% (0 d) Dark control	19.4 (10 d) Irradiated 94.3% (10 d) Dark control
					Natural water	89.6% (1 d) Irradiated 99.2% (0 d) Dark control	23.0 (10 d) Irradiated 81.0% (10 d) Dark control
			Soil photolysis	2522748	UK Sandy Clay Loam	104.7% (0 d) Irradiated 104.7% (0 d) Control	77.1% (15 d) Irradiated 62.7% (15 d) Control
			Aerobic soil metabolism	2522746	IL Silty Clay Loam	97.3% (0 d)	0.4% (120 d)
					WA Loam	96.5% (0 d)	0.6% (120 d)
					UK Clay/Clay Loam	57.7% (0 d)	1.1% (120 d)
				2522745	UK Sandy Clay Loam	90.7% (0 d)	0.9% (120 d)
			Anaerobic soil metabolism	2522747	UK Sandy Clay Loam	92.9% (0 d)	1.3% (120 d)
			Aerobic aquatic metabolism	2522755	Calwich Abbey Lake	94.7% (0 d)	ND (100 d)
					Swiss Lake	97.3% (0 d)	0.2% (100 d)
			Anaerobic aquatic metabolism	2522756	Calwich Abbey Lake	93.2% (0 d)	ND (100 d)
					Swiss Lake	95.5% (0 d)	3.1% (100 d)

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
	=C1OC(C)OC(=O)OC						
MAJOR (>10%) TRANSFORMATION PRODUCTS							
MT-2153	**IUPAC:** 1-ethyl-4-[4-methanesulfonyl-3-(2-methoxyethoxy)-2-methylbenzoyl]-1H-pyrazol-5-ol **Formula:** $C_{17}H_{22}N_2O_6S$ **MW:** 382.4 **SMILES:** CCN1N=CC(C(=O)C2=C(C)C(OCCOC)=C(C=C2)S(C)(=O)=O)=C1O		Hydrolysis	2603351	pH 4, 10°C	1.1% (30 d)	1.1% (30 d)
					pH 7, 10°C	7.8% (30 d)	7.8% (30 d)
					pH 9, 10°C	86.3% (7 d)	86.3% (7 d)
					pH 4, 25°C	7.1% (30 d)	7.1% (30 d)
					pH 7, 25°C	48.1% (30 d)	48.1% (30 d)
					pH 9, 25°C	97.2% (2 d)	97.2% (2 d)
					pH 4, 50°C	53.9% (30 d)	53.9% (30 d)
					pH 7, 50°C	88.9% (30 d)	88.9% (30 d)
					pH 9, 50°C	102.5% (0.33 d)	102.5% (0.33 d)
			Aqueous photolysis	2522753	Purified water	6.6% (7 d) Irradiated 5.8% (10 d) Dark Control	6.6% (7 d) Irradiated 5.8% (10 d) Dark Control
					Natural water	8.8% (10 d) Irradiated 26.6% (10 d) Dark Control	8.8% (10 d) Irradiated 26.6% (10 d) Dark Control
			Soil photolysis	2522748	UK Sandy Clay Loam	8.0% (13 d) Irradiated 74.2% (15 d) Control	5.4% (15 d) Irradiated 74.2% (15 d) Control
			Aerobic soil metabolism	2522746	IL Silty Clay Loam	54.0% (7 d)	9.5% (120 d)
					WA Loam	70.6% (7 d)	15.9% (120 d)
					UK Clay/Clay Loam	75.4% (3 d)	24.3% (120 d)
				2522745	UK Sandy Clay Loam	79.0% (0.5 d)	38.8% (120 d)
			Anaerobic soil metabolism	2522747	UK Sandy Clay Loam	86.4% (0.5 d)	57.3% (120 d)
			Aerobic aquatic metabolism	2522755	Calwich Abbey Lake	82.0% (8 d)	60.5% (100 d)
					Swiss Lake	80.9% (7 d)	61.9% (100 d)
			Anaerobic aquatic metabolism	2522756	Calwich Abbey Lake	89.3% (7 d)	71.4% (100 d)
					Swiss Lake	42.1% (3 d)	0.0% (100 d)

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
MMTA 3-(2-methoxyethoxy)-2-methyl-4-(methylsulfonyl)benzoic acid	**IUPAC:** 4-methanesulfonyl-3-(2-methoxyethoxy)-2-methylbenzoic acid **Formula:** $C_{12}H_{16}O_6S$ **MW:** 288.3 **SMILES:** COCCOC1=C(C=CC(C(O)=O)=C1C)S(C)(=O)=O		Aerobic soil metabolism	2522746	IL Silty Clay Loam	5.4% (7 d)	8.8% (120 d)
					WA Loam	10.4% (7 d)	2.0% (120 d)
					UK Clay/Clay Loam	6.7% (59 d)	3.0% (120 d)
					UK Sandy Clay Loam	ND	ND
EVC-006	Isomer A = Unk 15 (tentative)		Aqueous photolysis	2522753	Purified water	9.0% (7 d)	9.0% (7 d)
	Isomer B = Unk 17					11.8% (4 d)	10.4% (7 d)
	Isomers A and B					20.8%	19.4 (7 d)
	Isomer A = Unk 15 (tentative)				Natural water	6.5% (10 d)	6.5% (10 d)
	Isomer B = Unk 17					7.1% (10 d)	7.1% (10 d)
	Isomers A and B					13.6 (10 d)	13.6 (10 d)
EVC-005	Isomer A = Unk 16 (tentative)		Aqueous photolysis	2522753	Purified Water	10% (3 d)	7.1% (7 d)
	Isomer B = Unk 18					13.1% (2 d)	7.3% (7 d)
	Isomers A and B					23.1%	14.4 (7 d)
	Isomer A = Unk 16 (tentative)				Natural water	7.0% (7 d)	5.6% (10 d)
	Isomer B = Unk					7.3% (7 d)	6.4% (10 d)

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
	18						
	Isomers A and B					14.3 (7 d)	11.0 (10 d)
Carbon dioxide	**IUPAC:** Carbon dioxide **Formula:** CO_2 **MW:** 44 g/mol **SMILES:** C(=O)=O		Soil photolysis	2522748	UK Sandy Clay Loam	13.8% (15 d) Irradiated ND Control	13.8% (15 d) Irradiated ND Control
			Aerobic soil metabolism	2522746	IL Silty Clay Loam	9.7% (120 d)	9.7% (120 d)
					WA Loam	9.4% (120 d)	9.4% (120 d)
					UK Clay/Clay Loam	11.5% (120 d)	11.5% (120 d)
				2522745	UK Sandy Clay Loam	17.6% (120 d)	17.6% (120 d)
			Anaerobic soil metabolism	2522747	UK Sandy Clay Loam	ND	ND
			Aqueous photolysis	2522753	Purified Water	6.2% (7 d)	6.2% (7 d)
					Natural water	6.5% (10 d)	6.5% (10 d)
			Aerobic aquatic metabolism	2522755	Calwich Abbey Lake	0.6% (100 d)	0.6% (100 d)
					Swiss Lake	0.9% (100 d)	0.9% (100 d)
			Anaerobic aquatic metabolism	2522756	Calwich Abbey Lake	0.1% (100 d)	0.1% (100 d)
					Swiss Lake	0.3% (100 d)	0.3% (100 d)
Unk 14		unknown	Aqueous photolysis	2522753	Purified Water	17.1% (4 d)	11.7% (7 d)
					Natural water	7.0% (10 d)	7.0% (10 d)
Ph-A		unknown	Aerobic soil metabolism	2522746	WA Loam	15.7% (120 d)	15.7% (120 d)
					IL Silty Clay Loam	6.6% (120 d)	6.6% (120 d)
					UK Clay/Clay Loam	ND	ND (120 d)
				2522745	UK Sandy Clay Loam	ND	ND (120 d)
Unextracted residues	NA	unknown	Soil photolysis	2522748	UK Sandy Clay Loam	12.3% (10 d) Irradiated 17.8% (13 d) Control	8.7% (15 d) Irradiated 17.2% (15 d) Control
			Aerobic soil metabolism	2522746	IL Silty Clay Loam	79.4% (120 d)	79.4% (120 d)
					WA Loam	73.6% (59 d)	72.0% (120 d)
					UK Clay/Clay Loam	62.3% (120 d)	62.3% (120 d)
				2522745	UK Sandy Clay Loam	41.6% (120 d)	41.6% (120 d)
			Anaerobic soil	2522747	UK Sandy Clay Loam	41.3% (120 d)	41.3% (120 d)

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
			metabolism				
			Aerobic aquatic metabolism	2522756	Calwich Abbey Lake	29.6% (100 d)	29.6% (100 d)
					Swiss Lake	41.9% (100 d)	41.9% (100 d)
			Anaerobic aquatic metabolism	2522756	Calwich Abbey Lake	22.5% (100 d)	22.5% (100 d)
					Swiss Lake	9.8% (100 d)	22.5% (100 d)
MINOR (<10%) TRANSFORMATION PRODUCTS							
Deg A		unknown	Hydrolysis	2522752	pH 4, 10°C	ND	ND (30 d)
					pH 7, 10°C	0.5% (30 d)	0.5% (30 d)
					pH 9, 10°C	ND	ND (7 d)
					pH 4, 25°C	ND	ND (30 d)
					pH 7, 25°C	2.4% (10 d)	ND (30 d)
					pH 9, 25°C	ND	ND (2 d)
					pH 4, 50°C	1.4% (10 d)	ND (30 d)
					pH 7, 50°C	ND	ND (6 d)
					pH 9, 50°C	3.0% (0.010 d)	ND (0.333 d)
Deg B		unknown	Hydrolysis	2522752	pH 4, 10°C	ND	ND (30 d)
					pH 7, 10°C	0.4% (20 d)	ND (30 d)
					pH 9, 10°C	ND	ND (7 d)
					pH 4, 25°C	0.5% (10 d)	ND (30 d)
					pH 7, 25°C	ND	ND (30 d)
					pH 9, 25°C	ND	ND (2 d)
					pH 4, 50°C	ND	ND (30 d)
					pH 7, 50°C	ND	ND (6 d)
					pH 9, 50°C	ND	ND (0.333 d)
Unk 1		unknown	Aqueous photolysis	2522753	Purified water	4.3% (7 d)	4.3% (7 d)
					Natural water	5.5% (10 d)	5.5% (10 d)
Unk 2		unknown	Aqueous photolysis	2522753	Purified water	5.2% (7 d)	5.2% (7 d)
					Natural water	5.2% (10 d)	5.2% (10 d)
Unk 3		unknown	Aqueous photolysis	2522753	Purified water	7.9% (7 d)	7.9% (7 d)
					Natural water	7.1% (10 d)	7.1% (10 d)
Unk 4		unknown	Aqueous	2522753	Purified water	4.6% (7 d)	4.6% (7 d)

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
			photolysis		Natural water	6.4% (7 d)	6.2% (10 d)
Unk 5		unknown	Aqueous photolysis	2522753	Purified water	3.5% (7 d)	3.5% (7 d)
					Natural water	4.8% (7 d)	3.7% (10 d)
Unk 6		unknown	Aqueous photolysis	2522753	Purified water	1.4% (2 d)	0.5% (7 d)
					Natural water	7.0% (10 d)	7.0% (10 d)
Unk 7		unknown	Aqueous photolysis	2522753	Purified water	1.7% (3 d)	1.4% (7 d)
					Natural water	2.1% (10 d)	2.1% (10 d)
Unk 8		unknown	Aqueous photolysis	2522753	Purified water	1.6% (4 d)	1.0% (7 d)
					Natural water	3.8% (10 d)	3.8% (10 d)
Unk 9		unknown	Aqueous photolysis	2522753	Purified water	1.4% (7 d)	1.4% (7 d)
					Natural water	3.7% (10 d)	3.7% (10 d)
Unk 10		unknown	Aqueous photolysis	2522753	Purified water	3.4% (7 d)	3.4% (7 d)
					Natural water	1.4% (7 d)	1.3% (10 d)
Unk 11		unknown	Aqueous photolysis	2522753	Purified water	3.8% (7 d)	3.8% (7 d)
					Natural water	5.4% (2 d)	1.3% (10 d)
Unk 12		unknown	Aqueous photolysis	2522753	Purified water	1.9% (4 d)	0.9% (7 d)
					Natural water	5.6% (2 d)	1.0% (10 d)
Unk 13		unknown	Aqueous photolysis	2522753	Purified water	1.6% (1 d)	1.5% (7 d)
					Natural water	4.0% (10 d)	4.0% (10 d)
Unk 19		unknown	Aqueous photolysis	2522753	Purified water	3.5% (7 d) Irradiated 0.5% (7 d) Dark control	3.5% (7 d) Irradiated 0.5% (7 d) Dark control
					Natural water	3.6% (10 d) Irradiated 0.5% (1 d) Dark Control	3.6% (10 d) Irradiated 0.3 % (10 d) Dark Control
Unk 20		unknown	Aqueous photolysis	2522753	Purified water	5.2% (7 d)	5.2% (7 d)
					Natural water	n/a	n/a
Component 2		unknown	Soil photolysis	2522748	UK Sandy Clay Loam	1.2% (1 d) Irradiated ND Control	ND (15 d) Irradiated ND Control

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
Component 3		unknown	Soil photolysis	2522748	UK Sandy Clay Loam	2.9% (2 d) Irradiated ND Control	1.1% (15 d) Irradiated ND Control
Ph-B		unknown	Aerobic soil metabolism	2522746	IL Silty Clay Loam	ND	ND (120 d)
					WA Loam	ND	ND (120 d)
					UK Clay/Clay Loam	0.7% (30 d)	ND (120 d)
				2522745	UK Sandy Clay Loam	ND	ND (120 d)
Py-A		unknown	Aerobic soil metabolism	2522746	IL Silty Clay Loam	0.8% (30 d)	ND (120 d)
					WA Loam	1.7% (14 d)	ND (120 d)
					UK Clay/Clay Loam	ND	ND (120 d)
				2522745	UK Sandy Clay Loam	ND	ND (120 d)
Py-B		unknown	Aerobic soil metabolism	2522746	IL Silty Clay Loam	0.4% (59 d)	ND (120 d)
					WA Loam	ND	ND (120 d)
					UK Clay/Clay Loam	0.5% (30 d)	ND (120 d)
				2522745	UK Sandy Clay Loam	ND	ND (120 d)
Py-C		unknown	Aerobic soil metabolism	2522746	IL Silty Clay Loam	0.6% (120 d)	0.6% (120 d)
					WA Loam	ND	ND (120 d)
					UK Clay/Clay Loam	ND	ND (120 d)
				2522745	UK Sandy Clay Loam	ND	ND (120 d)
Met A		unknown	Aerobic soil metabolism	2522746	IL Silty Clay Loam	ND	ND (120 d)
					WA Loam	ND	ND (120 d)
					UK Clay/Clay Loam	ND	ND (120 d)
				2522745	UK Sandy Clay Loam	2.4% (30 d)	1.4% (120 d)
			Aerobic aquatic metabolism	2522755	Calwich Abbey Lake	3.4% (100 d)	3.4% (100 d)
					Swiss Lake	2.9% (30 d)	2.7% (100 d)
Met B		unknown	Aerobic soil metabolism	2522746	IL Silty Clay Loam	ND	ND (120 d)
					WA Loam	ND	ND (120 d)
					UK Clay/Clay Loam	ND	ND (120 d)
				2522745	UK Sandy Clay Loam	3.7% (30 d)	2.3% (120 d)
			Aerobic aquatic metabolism	2522755	Calwich Abbey Lake	0.2% (100 d)	0.2% (100 d)
					Swiss Lake	0.9% (100 d)	0.9% (100 d)

Code Name/ Synonym	Chemical Name	Chemical Structure	Study Type	PMRA #	Maximum %AR (day)		Final %AR (study length)
Polar Compound		unknown	Aerobic aquatic metabolism	2522755	Calwich Abbey Lake	0.2% (100 d)	0.2% (100 d)
					Swiss Lake	0.6% (100 d)	0.6% (100 d)

^AR means "applied radioactivity". MW means "molecular weight". ND means "not detected".

Table 12 Toxicity to Non-Target Species

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference PMRA #
Terrestrial species							
Invertebrates	Acute oral	Honey bee (*Apis mellifera*)	Tolpyralate	48-h LD_{50}	>107.7 µg a.i./bee	mortality	2522795
		Honey bee (*Apis mellifera* africanized)	SL-573 400SC	48-h LD_{50}	315 µg a.i./bee	mortality	2522838
		Bumble bee (*Bombus terrestris*)	Tolpyralate	48-h LD_{50}	>100 µg a.i./bee	mortality	2522796
	Acute contact	Honey bee (*Apis mellifera*)	Tolpyralate	48-h LD_{50}	>100.0 µg a.i./bee	mortality	2522795
		Honey bee (*Apis mellifera* africanized)	SL-573 400SC	48-h LD_{50}	>100 µg a.i./bee	mortality	2522839
		Bumble bee (*Bombus terrestris*)	Tolpyralate	48-h LD_{50}	>100.0 µg a.i./bee	mortality	2522796
		Earthworm (*Eisenia fetida*)	Tolpyralate	14-d LC_{50}	>1000 mg a.i./kg soil	mortality	2522801
			SL-573 400SC	14-d LC_{50}	>363 mg a.i./kg soil	mortality	2522840
		Parasitic wasp (*Aphidius rhopalosiphi*)	SL-573 100OD	48-h LR_{50}	>86.2 g a.i./ha	mortality	2581918
		Predatory mite (*Typhlodromus pyri*)	SL-573 100OD	7-d LR_{50}	>114.5 g a.i./ha	mortality	2581917
	Chronic adult*	Honey bee (Apis mellifera)	Tolpyralate	10-d NOED**	93 µg a.i./bee (3.2 µg a.i./µL)	mortality	2522766
	Acute larval	Honey bee (*Apis mellifera*)	Tolpyralate	8-d LD_{50}	74 µg a.i./bee	mortality	2735401

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference PMRA #
	Chronic larva	Honey bee (*Apis mellifera*)	Tolpyralate	22-d NOAEL	50 µg a.i./bee (330 µg a.i./g diet)	survival	2735401
	Reproduction	Earthworm (*Eisenia fetida*)	Tolpyralate	56-d NOEC	5 mg a.i./kg soil	reproduction	2522803
			MT-2153		25 mg a.i./kg soil	reproduction	2522802
			MMTA		100 mg a.i./kg soil	reproduction	2522804
		Collembola (*Folsomia candida*)	MT-2153	28-d NOEC	100 mg a.i./kg soil	reproduction	2522799
		Collembola (*Folsomia candida*)	MMTA	28-d NOEC	50 mg a.i./kg soil	reproduction	2522798
		Predatory mite (*Hypoaspis aculeifer*)	MT-2153	NOER	50 mg a.i./ha	reproduction	2522797
		Predatory mite (*Hypoaspis aculeifer*)	MMTA	NOER	100 mg a.i./ha	reproduction	2522800
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	Tolpyralate	LD_{50}	>2000 mg a.i./kg bw	mortality	2522758
		Mallard duck (*Anas platyrhynchos*)	Tolpyralate	LD_{50}	>2000 mg a.i./kg bw	mortality	2522759
		Zebra finch (*Taeniopygia guttata*)	Tolpyralate	LD_{50}	>2000 mg a.i./kg bw	mortality	2522757
	Dietary	Bobwhite quail (*Colinus virginianus*)	Tolpyralate	LC_{50}	>981 mg a.i./kg diet/day	mortality	2522760
		Mallard duck (*Anas platyrhynchos*)	Tolpyralate	LC_{50}	>1633mg a.i./kg diet/day	mortality	2522761
	Chronic	Bobwhite quail (*Colinus virginianus*)	Tolpyralate	NOEC	5 mg a.i./kg bw/day	reproduction	2522763
		Mallard duck (*Anas platyrhynchos*)	Tolpyralate	NOEC	14.2 mg a.i./kg bw/day	reproduction	2522762

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference PMRA #
Mammals	Acute oral	Rat	Tolpyralate	LD_{50}	>2000 mg a.i./kg bw	mortality	2523876
	Dietary	Rat	Tolpyralate	NOEL	1.34 mg a.i./kg diet	growth	
	Chronic (2-generation)	Rat	Reproduction	NOEL	3.57 mg a.i./kg bw	reproduction	
Plants	Seedling emergence	11 plant species	Seedling emergence	HC_5 of SSD for ER_{50}	1.5 g a.i. /ha	length	2522841
	Vegetative vigour		Vegetative vigour	HC_5 of SSD for ER_{50}	1 g a.i. /ha	weight	2522842
Freshwater Organisms							
Invertebrates	Acute	*Daphnia magna*	Tolpyralate	48-h EC_{50}	>19.5 mg a.i./L	immobility	2522778
			MT-2153	48-h EC_{50}	>104 mg a.i./L		2522780
			MMTA	48-h EC_{50}	>101 mg a.i./L		2603350
			SL-573 400SC	48-h EC_{50}	>195 mg a.i./L		2522779
	Chronic	*Daphnia magna*	Tolpyralate	21-d NOEC	8.96 mg a.i./L		2522781
		Chironomus riparius	MT-2153 (spiked sediment)	10-d NOEC	1000 mg a.i./kg dry sediment OR 662 mg a.i./L pore water	reproduction	2522788
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	Tolpyralate	96-h LC_{50}	>21.0 mg a.i./L	mortality	2522769
			MT-2153	96-h LC_{50}	>107 mg a.i./L	mortality	2522773
			MMTA	96-h LC_{50}	>101 mg a.i./L	mortality	2522774
			SL-573 400SC	96-h LC_{50}	>299 mg a.i./L	mortality	2522767
		Fathead minnow (*Pimephales promelas*)	Tolpyralate	96-h LC_{50}	>19.8 mg a.i./L	mortality	2522772
		Common carp (*Cyprinus carpio*)	Tolpyralate	96-h LC_{50}	>19 mg a.i./L	mortality	2522771

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect	Reference PMRA #
	Chronic (Early Life Stage)	Fathead minnow (*Pimephales promelas*)	Tolpyralate	34-d NOEC	0.0332 mg a.i./L	decreased weight (growth)	2522775
Algae	Acute	Green alga (*Pseudokirchneriella subcapitata*)	Tolpyralate	96-h EC_{50}	5.44 mg a.i./L	Yield	2522786
			MT-2153	72-h EC_{50} 72-h EC_{50}	2.4 mg a.i./L	Biomass yield	2522787
			MMTA		37.1 mg a.i./L		2617425
			SL-573 400SC	96-h EC_{50}	3.67 mg a.i./L	yield	2522837
		Anabaena flos-aquae	Tolpyralate	96-h EC_{50}	>19.6 mg a.i./L	reproduction	2522785
		Navicula pelliculosa	Tolpyralate	96-h EC_{50}	13.1 mg a.i./L	reproduction	2522782
Aquatic plant	Acute	*Myriophyllum spicatum*	MT-2153	14-d EC_{50}	36.6 µg a.i./L	dry weight	2522793
Vascular plants	Acute	Duckweed (*Lemna gibba*)	Tolpyralate	7-d EC_{50}	5.89 µg a.i./L	dry weight/yield	2522789
			MT-2153	7-d EC_{50}	2.14 µg a.i./L	dry weight/yield	2522791
			MMTA	7-d EC_{50}	>98.9 mg a.i./L	growth and yield	2522790
Marine/Estuarine organisms							
Invertebrates	Acute	Mysid shrimp (*Americamysis bahia*)	Tolpyralate	96-h LC_{50}	0.672 mg a.i./L	mortality	2522765
		Eastern oyster (*Crassostrea virginica*)		96-h IC_{50}	6.56 mg a.i./L	shell deposition	2522764
Algae	Acute	Marine diatom (*Skeletonema costatum*)	Tolpyralate	96-h IC_{50}	0.242 mg a.i./L	reproduction	2522784
Fish	Acute	Sheepshead minnow (*Cyprinodon variegates*)	Tolpyralate	96-h LC_{50}	>11.6 mg a.i./L	mortality	2522770

*ten-day non-guideline study on adult honey bees
**No Observed Effects Dose

Table 13* Species Sensitivity Distribution (SSDs) toxicity data analysis for Tolpyralate 400SC Herbicide: The HC_5[1] or the most sensitive endpoints are listed by taxonomic group for terrestrial crop plants[2].

Test material	Exposure	Terrestrial Plants (SE) EC_{25} (g a.i./ha)	Terrestrial Plants (SE) EC_{50} (g a.i./ha)	Terrestrial Plants (VV) EC_{25} (g a.i./ha)	Terrestrial Plants (VV) EC_{50} (g a.i./ha)
EP	Acute	HC_5: 0.5	HC_5: 1.5	HC_5: 0.12	HC_5: 1.0
		CI: 0.06-1.5 FA: 0.5-21%	CI: 0.19-4.4 FA: 0.4-23%	CI: 0.0029-0.8 FA: 0.4-23%	CI: 0.004-5.8 FA: 0.7-37%

(VV) = vegetative vigor; (SE) = seedling emergence; (CI) = lower and upper confidence level of HC_5; (FA) = fraction of species affected; EP = end-use product

* The most sensitive endpoint is derived from vegetative vigor based on the EC_{25} (HC_5 = 0.12 g a.i./ha) as listed in Table 1. Note that despite the accepted goodness of fit of the data to the model assumptions, the confidence intervals (CI) on the HC_5 and the fraction of species affected (FA) are relatively large, indicating high variability in the data set. For example, as a worst case scenario, up to 23% of all plants could be affected at an EC_{25} level of effect if exposed to 0.12 g a.i./ha of SL-573 400SC Herbicide. Similarly, using the EC50 data set, the HC_5 is 1.0 g a.i./ha, however, the lower CI is 0.004 g a.i./ha, and the higher CI on the FA is 37%, therefore, based on the data available, up to 37% of all plant species could be affected at the EC_{50} effect level in a worst case scenario.

[1]Hazardous concentration to 5% of species;

[2]Where SSDs could not be determined, the most sensitive species endpoint value is reported

Table 14 Screening Level Risk Assessment for Non-Target Terrestrial Invertebrates and Plants exposed to tolpyralate

Organism	Ecotox Endpoint Descriptor: Substance	Ecotox Endpoint Value	Converted Ecotox Endpoint Value[1]	Enviro Exposure (EEC) Value[2]	Enviro Exposure (EEC) Units	RQ	LOC Exceeded
TERRESTRIAL INVERTEBRATES							
Earthworm	Acute Mortality LC50	1000	500	0.0178	mg a.i./kg soil	$3.6x10^{-5}$	No
	Sub-lethal Effects NOEC	5	5	0.0178	mg a.i./kg soil	0.004	No
Honey bee (*Apis mellifera*)	Acute oral LD50	>107.7	>107.7	1.14	µg a.i./bee	<0.011	No
	Acute contact LD50	>100	>100	0.096	µg a.i./bee	<0.001	No
	Chronic adult NOED	93	93	1.14	µg a.i./bee	0.012	No
	Acute larval LD50	74	74	0.486	µg a.i./bee	0.007	No
	Chronic larval NOAEL	50	50	0.486	µg a.i./bee	0.009	No
Parasitic wasp	Acute LR50	>86.2	>43.1	55.16	g a.i./ha	<1.28	No
Predatory mite	Acute LR50	>114.5	>57.25	55.16	g a.i./ha	<0.964	No

Organism	Ecotox Endpoint Descriptor: Substance	Ecotox Endpoint Value	Converted Ecotox Endpoint Value[1]	Enviro Exposure (EEC) Value[2]	Enviro Exposure (EEC) Units	RQ	LOC Exceeded
TERRESTRIAL VASCULAR PLANTS							
Plants	Vegetative Vigour	HC_5 of SSC for ER_{50} value: 1.0 g a.i./ha	1	In-field: 55.16	g a.i./ha	55.2	Yes
				Off-field (ground appl., 6% drift): 3.31		3.31	Yes
	Seedling Emergence	HC_5 of SSC for ER_{50} value: 1.5 g a.i./ha	1.5	In-field: 40	g a.i./ha	26.7	Yes
				Off-field (ground appl., 6% drift): 2.4		1.60	Yes

[1] The uncertainty factor of ½ and 1/10 the EC_{50}/LC_{50} are used for acute endpoints. No uncertainty factors are applied to chronic endpoints.
[2] EEC calculations are based on the maximum label application rate of 40 g a.i./ha (applied twice) with a minimum application interval of 14 days between applications.

Table 15 Screening Level Risk Assessment for Non-Target Terrestrial Invertebrates exposed to MT-2153

Organism	Ecotox Endpoint Descriptor: Substance	Ecotox Endpoint Value	Converted Ecotox Endpoint Value[1]	Enviro Exposure (EEC) Value[2]	Enviro Exposure (EEC) Units	RQ	LOC Exceeded
TERRESTRIAL INVERTEBRATES							
Earthworm	Sub-lethal Effects NOEC	25	25	0.0284	mg a.i./kg soil	0.001	No
Collembola	NOEC	100	100	0.0284	mg a.i./kg soil	2.8×10^{-4}	No
Parasitic mite	Acute LR_{50}	50	25	45.0	g a.i./ha	1.80	No

[1] The uncertainty factor of ½ the EC_{50}/LC_{50} are used for acute endpoints. No uncertainty factors are applied to chronic endpoints.
[2] EEC calculations are based on 100% conversion of tolpyralate to MT-2153 immediately after application and using the molecular weight ratios of the MT-2153 to tolpyralate to obtain maximum application rate of 32.6 g MT-2153/ha (applied twice) with a minimum application interval of 14 days between applications.

Table 16 Screening Level Risk Assessment for birds

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ
Small Bird (0.02 kg)				
Acute	>200.00	Insectivore	4.49	<0.02
Reproduction	5.00	Insectivore	4.49	0.90
Medium Sized Bird (0.1 kg)				
Acute	>200.00	Insectivore	3.50	<0.02
Reproduction	5.00	Insectivore	3.50	0.70
Large Sized Bird (1 kg)				
Acute	>200.00	Herbivore (short grass)	2.26	<0.01
Reproduction	5.00	Herbivore (short grass)	2.26	0.45

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = $0.398(BW \text{ in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(BW \text{ in g})^{0.651}$.
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 17 Screening Level Risk Assessment for small terrestrial mammals.

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ
Small Mammal (0.015 kg)				
Acute	>200.00	Insectivore	2.58	<0.01
Reproduction	3.57	Insectivore	2.58	0.72
Medium Sized Mammal (0.035 kg)		Insectivore		
Acute	>200.00	Herbivore (short grass)	5.01	<0.03
Reproduction	3.57	Herbivore (short grass)	5.01	1.40
Large Sized Mammal (1 kg)				
Acute	>200.00	Herbivore (short grass)	2.68	<0.01
Reproduction	3.57	Herbivore (short grass)	2.68	0.75

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987).
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(BW \text{ in g})^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 18 Expanded screening Level Risk Assessment on reproduction for small wild mammals.

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-Field		On-field		Off-Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
Medium Sized Mammal (0.035 kg)										
Reproduction	3.57	Insectivore	2.26	0.634	0.07	0.019	1.56	0.438	0.05	0.013
	3.57	Granivore (grain and seeds)	0.35	0.098	0.01	0.003	0.17	0.047	0.01	0.001
	3.57	Frugivore (fruit)	0.70	0.196	0.02	0.006	0.33	0.0934	0.01	0.003
	3.57	Herbivore (short grass)	5.01	1.40*	0.15	0.042	1.78	0.498	0.05	0.015
	3.57	Herbivore (long grass)	3.06	0.857	0.09	0.026	1.00	0.280	0.03	0.008
	3.57	Herbivore (Broadleaf plants)	4.63	1.30*	0.14	0.039	1.53	0.430	0.05	0.013

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g)$^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.
*exceeds the level of concern of 1.0. All other calculated risk quotient values do not exceed the level of concern.

Table 19 Screening Level Risk Assessment for Non-Target Aquatic organisms exposed to tolpyralate

Organism	Ecotox Endpoint Descriptor	Ecotox Endpoint Value (mg a.i./L)	Converted Ecotox Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
FRESHWATER SPECIES						
Freshwater Pelagic Invertebrate: Water flea (*Daphnia magna*)	acute (48 hour EC_{50})	>19.5	>9.75	0.005	$<5.1x10^{-4}$	No
	chronic (21 day NOEC)	8.96	8.96	0.005	$5.6x10^{-4}$	No
Freshwater Benthic Invertebrate: Midge (*Chironomus riparius*)	chronic (10 day NOEC)	662	662	0.005	$1x10^{-5}$	No
Rainbow Trout (*Oncorhynchus mykiss*)	acute (96 hour LC_{50})	>21	>2.1	0.005	$<2.4x10^{-3}$	No
Fathead minnow (*Pimephales promelas*)	acute (96 hour LC_{50})	>19.8	>1.98	0.005	$<2.5x10^{-3}$	No
	chronic (34 d NOEC)	0.0332	0.0332	0.005	$1.7x10^{-2}$	No
Common carp (*Cyprinus carpio*)	acute yield (96 hour EC_{50})	>19	>1.9	0.005	$<2.6x10^{-3}$	No
Freshwater Green Alga (*Pseudokirchneriella subcapitata*)	acute yield (96 hour EC_{50})	5.44	2.72	0.005	$1.9x10^{-3}$	No
Freshwater Blue-green Alga (*Anabaena flos-aquae*)	acute reproduction (96 hour EC_{50})	>19.6	>9.8	0.005	$<5.1x10^{-4}$	No
Freshwater diatom (*Navicula pelliculosa*)	acute reproduction (96 hour EC_{50})	13.10	6.55	0.005	$7.7x10^{-4}$	No
Freshwater Macrophyte (*Lemna gibba G3*)	acute dry weight/yield (7-d EC_{50})	0.00589	0.00295	0.005	1.70	Yes
Aquatic plant (*Myriophyllum spicatum*)	acute (14-d EC50)	0.0366	0.0183	0.005	0.27	No

Organism	Ecotox Endpoint Descriptor	Ecotox Endpoint Value (mg a.i./L)	Converted Ecotox Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
Amphibians (fish data used as surrogate)	Common carp (LC_{50})	>19	>1.9	0.03	$<1.4x10^{-2}$	No
	Fathead minnow ELS (NOEC)	0.0332	0.0332	0.03	$8.8x10^{-2}$	No
MARINE SPECIES						
Marine Invertebrate: Mysid shrimp (*Americamysis bahia*)	acute (96 hour EC_{50})	0.672	0.336	0.005	$1.5x10^{-2}$	No
Marine Invertebrate: Eastern oyster (*Crassostrea virginica*)	acute (96 hour LI_{50})	6.56	3.28	0.005	$1.5x10^{-3}$	No
Marine Fish: Sheepshead minnow (*Cyprinodon variegatus*)	acute (96 hour EC_{50})	>11.6	>5.8	0.005	$<8.7x10^{-4}$	No
Marine alga: Diatom (*Skeletonema costatum*)	acute reproduction (96 hour EC_{50})	0.242	0.121	0.005	$4.1x10^{-2}$	No

[1] The uncertainty factor of ½ and 1/10 the EC_{50}/LC_{50} are used for acute endpoints. No uncertainty factors are applied to chronic endpoints.

[2] EEC calculations are based on the maximum label application rate of 40 g a.i./ha (applied twice) with a minimum application interval of 14 days between applications. The EEC for aquatic organisms are based on a water depth of 80 cm while the EEC for amphibians are based on a depth of 15 cm.

Table 20 Screening Level Risk Assessment for Non-Target Aquatic organisms exposed to MT-2153

Organism	Ecotox Endpoint Descriptor	Ecotox Endpoint Value (mg a.i./L)	Converted Ecotox Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
FRESHWATER SPECIES						
Freshwater Pelagic Invertebrate: Water flea (*Daphnia magna*)	acute (48 hour EC_{50})	>104	>52	0.008	$<1.5x10^{-4}$	No
Rainbow Trout (*Oncorhynchus mykiss*)	acute (96 hour LC_{50})	>107	>10.7	0.008	$<7.0x10^{-4}$	No

Organism	Ecotox Endpoint Descriptor	Ecotox Endpoint Value (mg a.i./L)	Converted Ecotox Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
Freshwater Green Alga (*Pseudokirchneriella subcapitata*)	acute yield (96 hour EC_{50})	2.4	1.2	0.008	$6.6x10^{-3}$	No
Freshwater Macrophyte (*Lemna gibba G3*)	acute dry weight/yield (7-d EC_{50})	0.00214	0.00107	0.008	7.45	Yes
Amphibians (fish data used as surrogate)	Rainbow trout acute (LC_{50})	>107	>10.7	0.043	$<4.0x10^{-3}$	No

[1] The uncertainty factor of ½ the EC_{50}/LC_{50} are used for acute endpoints. No uncertainty factors are applied to chronic endpoints.

[2] EEC calculations are based on 100% conversion of tolpyralate to MT-2153 immediately after application and using the molecular weight ratios of the MT-2153 to tolpyralate to obtain maximum application rate of 32.6 g MT-2153/ha (applied twice) with a minimum application interval of 14 days between applications. The EEC for aquatic organisms are based on a water depth of 80 cm while the EEC for amphibians are based on a depth of 15 cm.

Table 21 Refined Risk Assessment on Non-Target aquatic organisms (*Lemna gibba*)

Organism	Ecotox Endpoint Descriptor	Ecotox Endpoint Value (mg a.i./L)	Converted Ecotox Value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC Exceeded
Tolpyralate						
Freshwater Macrophyte (*Lemna gibba G3*)	acute dry weight/yield (7-d EC50)	0.00589	0.002945	0.0005	$2.4x10^{-5}$	No
MT-2153						
Freshwater Macrophyte (*Lemna gibba G3*)	acute dry weight/yield (7-d EC50)	0.00214	0.00107	0.003	2.43	Yes

Table 22 List of Supported Uses

Items	Supported use claims
Application rate	Apply 30-40 g a.i./ha + 1% MSO + 12.5-25 L/1000 L spray solution of a high quality urea ammonium nitrate (UAN) or 8.4-20.4 kg/1000 L of a spray grade ammonium sulfate (AMS) if desired
Number of applications	One or two

Items	Supported use claims
Tankmix partner	Atrazine (minimum of 0.56 kg a.i./ha)
Efficacy claims	Control or suppression of the following weeds: Palmer amaranth, common cocklebur, lamb's quarters, redroot pigweed, smooth pigweed, green pigweed, common purslane, common ragweed, giant ragweed, shepherd's purse, Pennsylvania smartweed, common waterhemp, tall waterhemp, barnyardgrass, large crabgrass, giant foxtail, green foxtail, yellow foxtail.
Hosts and use sites	Field corn, seed corn, sweet corn, popcorn.
Use methods	Ground application by conventional methods (boom sprayer) in 140-470 L/ha water. Post-emergence to the crop and weeds. Up to the 6 leaf stage of corn. Rainfast in one hour.
Rotational crops	Immediate: corn, field, seed, sweet and pop. 3 months: winter wheat and rye (annual and fall) 9 months: alfalfa, dry bean, green bean, cabbage, canola (rapeseed), peas (field and edible), peanut, potato, snap beans, sorghum, soybean, cucurbits, sunflower, tomato, spring wheat, barley, oats 12 months: all other crops 18 months: sugarbeets

Table 23 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products (MT-2153) Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	0.92	207
	Water	Half-life ≥ 182 days	1.77	206
	Sediment	Half-life ≥ 365 days	not available	not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Not determined	Not determined

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active Ingredient Endpoints	Transformation Products (MT-2153) Endpoints
Bioaccumulation[4]	Log $K_{OW} \geq 5$	1.9	1.72[5]
	BCF $\geq$ 5000	not available	
	BAF $\geq$ 5000	not available	
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).
[5]USEPA. 2012. EPISuite Estimation Programs Interface Suite. KOWWIN v1.68.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Tolpyralate is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for tolpyralate in Canada are the same as corresponding tolerances to be promulgated in the United States, except for livestock commodities, in accordance with Table 1.

Once established, the American tolerances for tolpyralate will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[9] listed for tolpyralate in or on any commodity on the Codex Alimentarius Pesticide Residues in Food and Feed website.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Field corn; popcorn grain; sweet corn cars plus cobs with husks removed	0.01	0.01	Not Established
Eggs; fat, meat and meat byproducts of cattle, goat, hog, horse, poultry and sheep; milk	0.02	Not established	Not Established

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

[9] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

Appendix III Aquatic Ecoscenario Assessment

Aquatic Ecoscenario Assessment: Level 1 Modelling

For Level 1 aquatic ecoscenario assessment, estimated environmental concentrations (EECs) of tolpyralate and MT-2153 from runoff into a receiving water body was simulated using the PWC (Pesticide in Water Calculator) model. The PWC model simulates pesticide runoff from a treated field into an adjacent water body and the fate of the pesticide within that water body. For the Level 1 assessment, the water body consists of a 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha. A seasonal water body was also used to assess the risk to amphibians, as a risk was identified at the screening level. This water body is a scaled-down version of the permanent water body noted above, but having a water depth of 0.15 m.

Five standard regional scenarios, Rasp-BC, Potato-MB, Corn-ON, Corn-QC and Potato-PEI, were modelled to represent the use on corn in different regions of Canada. A number of initial application dates between May and July were modelled for each scenario. Table 1 lists the application information and the main environmental fate characteristics used in the simulations. The EECs are for the portion of the pesticide that enters the water body via runoff only; deposition from spray drift is not included. The model was run for 50 years for all scenarios.

The EECs are calculated from the model output from each run as follows. For each year of the simulation, PWC calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96-hour, 21-day, 60-day, 90-day, and 1 year). The 90th percentiles over each averaging period are reported as the EECs for that period.

The largest EECs from the initial application dates modelled are shown in Table 1 and 2 for the 80-cm deep water body and in tables Table 3 and 4 for the 15-cm water body.

Table 1 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for tolpyralate in a water body 0.8-m deep, excluding spray drift

Region	Water column EEC					
	Peak	96-hour	21-day	60-day	90-day	Yearly
BC	0.057	0.035	0.010	0.004	0.003	0.0007
Prairie	0.44	0.26	0.073	0.026	0.018	0.004
ON	0.57	0.31	0.094	0.035	0.023	0.002
QC	0.42	0.25	0.069	0.026	0.017	0.002
Atlantic	0.73	0.50	0.16	0.057	0.038	0.009
Maximum	0.73	0.50	0.16	0.057	0.038	0.009

Table 2 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for MT-2153 in a water body 0.8-m deep, excluding spray drift

Region	Water column EEC					
	Peak	96-hour	21-day	60-day	90-day	Yearly
BC	0.17	0.17	0.17	0.17	0.17	0.11
Prairie	2.6	2.6	2.5	2.5	2.6	1.8
ON	2.6	2.6	2.5	2.5	2.4	1.7
QC	2.6	2.6	2.5	2.3	2.2	1.2
Atlantic	2.6	2.6	2.6	2.6	2.7	2.2
Maximum	2.6	2.6	2.6	2.6	2.7	2.2

Table 3 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for tolpyralate in a water body 0.15-m deep, excluding spray drift

Region	Water column EEC					
	Peak	96-hour	21-day	60-day	90-day	Yearly
BC	0.30	0.18	0.050	0.020	0.014	0.003
Prairie	2.3	1.3	0.37	0.13	0.088	0.010
ON	3.0	1.6	0.47	0.18	0.12	0.029
QC	2.2	1.3	0.35	0.13	0.086	0.021
Atlantic	3.9	2.6	0.79	0.28	0.19	0.017
Maximum	3.9	2.6	0.79	0.28	0.19	0.029

Table 4 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for MT-2153 in a water body 0.15-m deep, excluding spray drift

Region	Water column EEC					
	Peak	96-hour	21-day	60-day	90-day	Yearly
BC	0.74	0.73	0.68	0.57	0.57	0.42
Prairie	11	11	10	8.8	8.7	6.6
ON	11	11	10	9.0	8.9	6.0
QC	11	11	11	9.0	8.2	6.0
Atlantic	9.6	9.5	9.2	9.3	9.4	3.7
Maximum	11	11	11	9.3	9.4	6.6

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A. List of Studies/Information Submitted by Registrant

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	IA 2.1,IIIA 2.11,IIIA 2.12,IIIA 2.13,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.3.2,IIIA 2.4.1,IIIA 2.5.2,IIIA 2.6.1,IIIA 2.7.5
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2522788	2015, Effects of MT-2153 on the Development of *Chironomus riparius* in a Sediment-Water System - Exposed Via Spiked Sediment, DACO: 9.9,IIA 8.5.2
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2522791	2015, Toxicity of MT-2153 to the Aquatic Plant *Lemna gibba* in a Static Growth Inhibition Test, DACO: 9.8.5,IIA 8.6
2522792	2014, Toxicity of SL-573 TGAI to the Aquatic Plant *Myriophyllum aquaticum* in a Static Growth Inhibition Test with a Prior Rooting Phase, DACO: 9.8.5,IIA 8.6
2522793	2015, Toxicity of MT-2153 to the Aquatic Plant *Myriophyllum spicatum* in a Static Growth Inhibition Test with a Prior Rooting Phase, DACO: 9.8.5,IIA 8.6
2522795	2013, Effects of SL-573 TGAI (Acute Contact and Oral) on Honey Bees (*Apis mellifera* L.) in the Laboratory, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2
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2522797	2014, Effects of MT-2153 on Reproduction of the Predatory Mite *Hypoaspis aculeifer* in Artificial Soil with 5% Peat, DACO: 9.2.5,IIA 8.8.1.2
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2522803	2014, Effects of SL-573 TGAI on Reproduction and Growth of Earthworms *Eisenia fetida* in Artificial Soil with 5% Peat, DACO: 9.2.3.1,IIA 8.9.2
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2522838	2014, Acute Oral Toxicity of SL-573 400 SC (SL-573 40% SC) to Honeybee *Apis mellifera* (Africanized), DACO: 9.2.8,IIIA 10.4.2.1,IIIA 10.4.2.2
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2522840	2014, Acute Toxicity of SL-573 400SC to the Earthworm *Eisenia fetida* in Artificial Soil with 5% Peat, DACO: 9.2.8,IIIA 10.6.2
2522841	2014, Effects of SL-573 400SC on Terrestrial (Non-Target) Plants: Seedling Emergence and Seedling Growth Test, DACO: 9.8.6,IIIA 10.8.1.1
2522842	2014, Effects of SL-573 400SC on Terrestrial (Non-Target) Plants: Vegetative Vigour Test, DACO: 9.8.6,IIIA 10.8.1.2
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2603481	2015, Amended Report Algae Growth Inhibition Study of SL-573 400SC in *Pseudokirchneriella subcapitata*, DACO: 9.3.2

4.0 Value

2522852	2012, Corn Efficacy, DACO: 10.2.3.4
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2522985 2015, Corn Efficacy, DACO: 10.2.3.4
2522986 2015, Corn Efficacy, DACO: 10.2.3.4
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B. Additional Information Considered

i) Published Information

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